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=> d que stat l13
L1             3 SEA FILE=REGISTRY ABB=ON  ACTIVIN/CN
L2        233478 SEA FILE=HCAPLUS ABB=ON  ?TRANSCRIPT?(L)(?REPRES? OR ?FACTOR?
                 OR ?REGULAT?)
L3          4862 SEA FILE=HCAPLUS ABB=ON  L2 AND (?SMAD?(W)(?PROTEIN? OR
                 ?REPRESSOR?) OR DNA?(W)?BIND?(W)?PROTEIN?)
L4           847 SEA FILE=HCAPLUS ABB=ON  L3 AND (TGF-BETA OR L1 OR ?ACTIVIN?
                 OR ?DROSOPHILA?)
L9            19 SEA FILE=HCAPLUS ABB=ON  L4 AND (?CTBP? OR ?DCTBP? OR ?CTBP2?
                 OR EVI(W)1 OR ?GGIF? OR ?SIP1? OR ?SCHNURRI?)
L10            6 SEA FILE=HCAPLUS ABB=ON  L9 AND (MAD? OR ?MEDEA?)
L11           19 SEA FILE=HCAPLUS ABB=ON  L9 OR L10
L12            6 SEA FILE=HCAPLUS ABB=ON  L11 AND (?METHOD? OR ?TECHNIQ? OR
                 ?PROCES?)
L13           19 SEA FILE=HCAPLUS ABB=ON  L11 OR L12


=> d ibib abs l13 1-19

L13  ANSWER 1 OF 19  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2004:449884  HCAPLUS
DOCUMENT NUMBER:          140:420388
TITLE:                    Binary prediction tree modeling with many predictors
                          and its uses in clinical and genomic applications
INVENTOR(S):              Nevins, Joseph R.; West, Mike; Huang, Andrew T.
PATENT ASSIGNEE(S):       Duke University, USA
SOURCE:                   PCT Int. Appl., 886 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   5
PATENT INFORMATION:

     PATENT NO.         KIND  DATE           APPLICATION NO.   DATE
     ---------------    ----  --------       ---------------   --------
     WO 2004038376      A2    20040506       WO 2003-XB33946   20031024
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
             GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
             LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,
             OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
             TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ,
             BY, KG, KZ, MD
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
             CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
             NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
             GW, ML, MR, NE, SN, TD, TG
     WO 2004038376      A2    20040506       WO 2003-US33946   20031024
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
             GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
             LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,
             OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
             TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ,
             BY, KG, KZ, MD
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
             CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
             NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
             GW, ML, MR, NE, SN, TD, TG
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PRIORITY APPLN. INFO.:

US 2002-420729P	P	20021024
US 2002-421062P	P	20021025
US 2002-421102P	P	20021025
US 2002-424701P	P	20021108
US 2002-424715P	P	20021108
US 2002-424718P	P	20021108
US 2002-425256P	P	20021112
US 2003-448461P	P	20030221
US 2003-448462P	P	20030221
US 2003-457877P	P	20030327
US 2003-458373P	P	20030331
WO 2003-US33946	A	20031024

AB The statistical anal. described and claimed is a predictive statistical tree model that overcomes several problems observed in prior statistical models and regression analyses, while ensuring greater accuracy and predictive capabilities. Although the claimed use of the predictive statistical tree model described herein is directed to the prediction of a disease in individuals, the claimed model can be used for a variety of applications including the prediction of disease states, susceptibility of disease states or any other biol. state of interest, as well as other applicable non-biol. states of interest. This model first screens genes to reduce noise, applies kmeans correlation-based clustering targeting a large number of clusters, and then uses singular value decompns. (SVD) to extract the single dominant factor (principal component) from each cluster. This generates a statistically significant number of cluster-derived singular factors, that are referred to as metagenes, that characterize multiple patterns of expression of the genes across samples. The strategy aims to extract multiple such patterns while reducing dimension and smoothing out gene-specific noise through the aggregation within clusters. Formal predictive anal. then uses these metagenes in a Bayesian classification tree anal. This generates multiple recursive partitions of the sample into subgroups (the 'leaves' of the classification tree), and assocs. Bayesian predictive probabilities of outcomes with each subgroup. Overall predictions for an individual sample are then generated by averaging predictions, with appropriate wts., across many such tree models. The model includes the use of iterative out-of-sample, cross-validation predictions leaving each sample out of the data set one at a time, refitting the model from the remaining samples and using it to predict the hold-out case. This rigorously tests the predictive value of a model and mirrors the real-world prognostic context where prediction of new cases as they arise is the major goal.

L13 ANSWER 2 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:371064 HCAPLUS
DOCUMENT NUMBER: 140:373461
TITLE: Evaluation of breast cancer states and outcomes using gene expression profiles
INVENTOR(S): West, Mike; Nevins, Joseph R.; Huang, Andrew
PATENT ASSIGNEE(S): Synpac, Inc., USA
SOURCE: PCT Int. Appl., 799 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004037996	A2	20040506	WO 2003-US33656	20031024

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT,
TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ,
MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG

US 2004083084	A1	20040429	US 2002-291878	20021112
US 2004106113	A1	20040603	US 2002-291886	20021112

PRIORITY APPLN. INFO.:

US 2002-420729P	P	20021024
US 2002-421062P	P	20021025
US 2002-421102P	P	20021025
US 2002-424701P	P	20021108
US 2002-424715P	P	20021108
US 2002-424718P	P	20021108
US 2002-291878	A	20021112
US 2002-291886	A	20021112
US 2002-425256P	P	20021112
WO 2002-US38216	A	20021112
WO 2002-US38222	A	20021112
US 2003-448461P	P	20030221
US 2003-448462P	P	20030221
US 2003-457877P	P	20030327
US 2003-458373P	P	20030331

AB The present invention relates generally to a **method** for evaluating and/or predicting breast cancer states and outcomes by measuring gene and metagene expression levels and integrating such data with clin. risk factors. Genes and metagenes whose expressions are correlated with a particular breast cancer risk factor or phenotype are provided using binary prediction tree modeling. The invention provides 175 genes associated with metagene predictors of lymph node metastasis, 216 genes associated with metagene predictors of breast cancer recurrence, and 496 metagenes related to breast cancer study. **Methods** of using the subject genes and metagenes in diagnosis and treatment **methods** , as well as drug screening **methods**, etc are also provided. In addition, reagents, media and kits that find use in practicing the subject **methods** are also provided.

L13 ANSWER 3 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:270511 HCAPLUS
DOCUMENT NUMBER: 141:66924
TITLE: Isolation and characterization of the Xenopus HIVEP gene family
AUTHOR(S): Duerr, Ulrike; Henningfeld, Kristine A.; Hollemann, Thomas; Knoechel, Walter; Pieler, Tomas
CORPORATE SOURCE: Abteilung Entwicklungsbiochemie, Universitaet Goettingen, Goettingen, 37077, Germany
SOURCE: European Journal of Biochemistry (2004), 271(6), 1135-1144
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The HIVEP gene family encodes for very large sequence-specific **DNA binding proteins** containing multiple zinc fingers. Three mammalian paralogous genes have been identified, HIVEP1, -2 and -3, as well as the closely related **Drosophila** gene, **Schnurri**.

These genes have been found to directly participate in the **transcriptional regulation** of a variety of genes. Mammalian HIVEP members have been implicated in signaling by TNF-α and in the pos. selection of thymocytes, while **Schnurri** has been shown to be an essential component of the **TGF**-β signaling pathway. In this study, we describe the isolation of Xenopus HIVEP1, as well as partial cDNAs of HIVEP2 and -3. Anal. of the temporal and spatial expression of the XHIVEP **transcripts** during early embryogenesis revealed ubiquitous expression of the **transcripts**. Assays using Xenopus oocytes mapped XHIVEP1 domains that are responsible for nuclear export and import activity. The DNA binding specificity of XHIVEP was characterized using a PCR-mediated selection and gel mobility shift assays.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:190765 HCAPLUS
DOCUMENT NUMBER: 140:421933
TITLE: Pleiotropic and diverse expression of ZFHX1B gene transcripts during mouse and human development supports the various clinical manifestations of the "Mowat-Wilson" syndrome
AUTHOR(S): Bassez, Guillaume; Camand, Olivier J. A.; Cacheux, Valere; Kobetz, Alexandra; Dastot-Le Moal, Florence; Marchant, Dominique; Catala, Martin; Abitbol, Marc; Goossens, Michel
CORPORATE SOURCE: INSERM U468 et Serv. Biochim. Genet., Hopital Henri Mondor, Creteil, Fr.
SOURCE: Neurobiology of Disease (2004), 15(2), 240-250
CODEN: NUDIEM; ISSN: 0969-9961
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB ZFHX1B encodes Smad-interacting protein 1, a **transcriptional corepressor** involved in the transforming growth **factors** β (**TGF**β) signaling pathway. ZFHX1B mutations cause a complex developmental phenotype characterized by severe mental retardation (MR) and multiple congenital defects. The authors compared the distribution of ZFHX1B **transcripts** during mouse and human embryogenesis as well as in adult mice and humans. This showed that this gene is strongly transcribed at an early stage in the developing peripheral and central nervous systems of both mice and humans, in all neuronal regions of the brains of 25-wk human fetuses and adult mice, and at varying levels in numerous nonneural tissues. Northern blot anal. suggested that ZFHX1B undergoes tissue-specific alternative splicing in both species. These results strongly suggest that ZFHX1B dets. the **transcriptional** levels of target genes in various tissues through the combinatorial interactions of its isoforms with different **Smad proteins**. Thus, as well as causing neural defects, ZFHX1B mutations may also cause other malformations.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:532691 HCAPLUS
DOCUMENT NUMBER: 139:95435
TITLE: Modified receptors on cell membranes for the discovery of therapeutic ligands
INVENTOR(S): Schwartz, Thue W.; Martini, Lene; Heydorn, Arne;

Jorgensen, Rasmus
PATENT ASSIGNEE(S): 7TM Pharma A/S, Den.
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055914	A2	20030710	WO 2002-DK900	20021220
WO 2003055914	A3	20031023		

W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

DK 2001-1944	A	20011221
DK 2002-113	A	20020122
DK 2002-1043	A	20020703
US 2002-394122P	P	20020703

AB A drug discovery **method** is provided for selecting a compound selected from the group consisting of a small organic substance, a biopharmaceutical, or an antibody or part thereof. The **method** comprises the steps of (i) expressing one or more receptors on a cell membrane, such as, e.g., an exterior cell surface of a cell, (ii) contacting one or more expressed receptors with a test compound or a selection of test compds. (libraries), and (iii) selecting one or more compds. based on its ability to bind one or more receptors. The step of expressing the one or more receptors comprises capturing one or more receptors on the exterior cell surface in a conformation that predominantly enables binding or interaction with a ligand, and the conformation that predominantly enables binding or interaction with a ligand is provided by modification of one or more receptors by a **method** comprising at least one of the following: (a) fusion with any protein which keeps the receptor in the desired conformation such as, e.g. an arrestin, a modified arrestin, a G-protein or a modified G-protein, (b) site-directed mutagenesis, and (c) deletion. The receptors may be captured on the exterior cell surface by at least one of the following: (d) interaction of the receptor with a scaffolding protein, optionally, with a scaffolding protein network and (e) means for blocking receptor internalization, e.g. by co-expression of a mutated dynamin or a modified arrestin or by use of chems. such as, e.g., sucrose and/or Tris. Thus, by coexpressing of either the wild-type receptor or by modifying the receptor by engineering for example a recognition motif for a strong binder into its structure (for example, a PDZ recognition motif at its C-terminal end), and coexpression of this with a scaffolding protein such as PSD-95 or a modified scaffolding protein which interacts with the cytoskeleton at the cell surface or is **made** to be closely associated with the membrane through a lipid anchor, a high level of surface expression can be ensured, which will benefit its use in the drug discovery **process**. As a result of the strong tendency of the scaffolding proteins to interact with each other, just the cotransfection

with one or more appropriate scaffolding proteins or modified scaffolding protein may also lead to the formation of patches with high local concns of the receptor or modified receptor, which will be highly beneficial in the drug discovery **process** where they are used initially to select binding mols. The **method** is exemplified by expression of the NK1 receptor in an agonist high-affinity binding form at the surface of transfected cells through fusion with arrestin or the N-terminal fragment of arrestin.

L13 ANSWER 6 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:389319 HCAPLUS
DOCUMENT NUMBER: 139:144804
TITLE: Regulation of Smad signaling through a differential recruitment of coactivators and corepressors by ZEB proteins
AUTHOR(S): Postigo, Antonio A.; Depp, Jennifer L.; Taylor, Jennifer J.; Kroll, Kristen L.
CORPORATE SOURCE: Division of Molecular Oncology, Department of Internal Medicine, Washington Univ. Sch. Med., St. Louis, MO, 63110, USA
SOURCE: EMBO Journal (2003), 22(10), 2453-2462
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Balancing signals derived from the **TGFβ** family is crucial for **regulating** cell proliferation and differentiation, and in establishing the embryonic axis during development. **TGF. beta.**/BMP signaling leads to the activation and nuclear translocation of **Smad proteins**, which activate **transcription** of specific target genes by recruiting P/CAF and p300. The two members of the ZEB family of zinc finger **factors** (ZEB-1/δEF1 and ZEB-2/ **SIP1**) **regulate TGF** β /BMP signaling in opposite ways: ZEB-1/δEF1 synergizes with Smad-mediated **transcriptional** activation, while ZEB-2/**SIP1 represses** it. Here the authors report that these antagonistic effects by the ZEB proteins arise from the differential recruitment of **transcriptional** coactivators (p300 and P/CAF) and **corepressors** (**CtBP**) to the Smads. Thus, while ZEB-1/δEF1 binds to p300 and promotes the formation of a p300-Smad **transcriptional** complex, ZEB-2/**SIP1** acts as a **repressor** by recruiting **CtBP**. This model of **regulation** by ZEB proteins also functions in vivo, where they have opposing effects on the **regulation** of **TGF.beta** . family-dependent genes during Xenopus development.
REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:389318 HCAPLUS
DOCUMENT NUMBER: 139:131160
TITLE: Opposing functions of ZEB proteins in the regulation of the **TGFβ** /BMP signaling pathway
AUTHOR(S): Postigo, Antonio A.
CORPORATE SOURCE: Department of Internal Medicine, Division of Molecular Oncology, Washington University School of Medicine, St Louis, MO, 63110, USA
SOURCE: EMBO Journal (2003), 22(10), 2443-2452
CODEN: EMJODG; ISSN: 0261-4189

PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Binding of **TGFβ** /BMP **factors** to their receptors leads to translocation of **Smad proteins** to the nucleus where they activate **transcription** of target genes. The two-handed zinc finger proteins encoded by Zfhx1a and Zfhx1b, ZEB-1/δEF1 and ZEB-2/ **SIP1**, resp., **regulate** gene expression and differentiation programs in a number of tissues. Here I demonstrate that ZEB proteins are also crucial **regulators** of **TGFβ** /BMP signaling with opposing effects on this pathway. Both ZEB proteins bind to Smads, but while ZEB-1/δEF1 synergizes with **Smad proteins** to activate **transcription**, promote osteoblastic differentiation and induce cell growth arrest, the highly related ZEB-2/**SIP1** protein has the opposite effect. Finally, the ability of **TGF.beta** . to mediate **transcription** of **TGF.beta** .-dependent genes and induce growth arrest depends on the presence of endogenous ZEB-1/δEF1 protein.
REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 8 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:228825 HCAPLUS
DOCUMENT NUMBER: 139:48729
TITLE: **Transcription factor** YY1 functions as a PcG protein in vivo
AUTHOR(S): Atchison, Lakshmi; Ghias, Ayesha; Wilkinson, Frank; Bonini, Nancy; Atchison, Michael L.
CORPORATE SOURCE: Department of Biology, Chestnut Hill College, Philadelphia, PA, 19118, USA
SOURCE: EMBO Journal (2003), 22(6), 1347-1358
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Polycomb group (PcG) proteins function as high mol. weight complexes that maintain **transcriptional repression** patterns during embryogenesis. The vertebrate **DNA binding protein** and **transcriptional repressor**, YY1, shows sequence homol. with the **Drosophila** PcG protein, pleiohomeotic (PHO). YY1 might therefore be a vertebrate PcG protein. We used **Drosophila** embryo and larval/imaginal disk **transcriptional repression** systems to determine whether YY1 **repressed transcription** in a manner consistent with PcG function in vivo. YY1 **repressed transcription** in **Drosophila**, and this **repression** was stable on a PcG-responsive promoter, but not on a PcG-non-responsive promoter. PcG mutants ablated YY1 **repression**, and YY1 could substitute for PHO in **repressing transcription** in wing imaginal disks. YY1 functionally compensated for loss of PHO in pho mutant flies and partially corrected mutant phenotypes. Taken together, these results indicate that YY1 functions as a PcG protein. Finally, we found that YY1, as well as Polycomb, required the co-**repressor** protein **CtBP** for **repression** in vivo. These results provide a mechanism for recruitment of vertebrate PcG complexes to DNA and demonstrate new functions for YY1.
REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 9 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:937303 HCAPLUS
DOCUMENT NUMBER: 138:20443
TITLE: Endocrine disruptor screening using DNA chips of endocrine disruptor-responsive genes
INVENTOR(S): Kondo, Akihiro; Takeda, Takeshi; Mizutani, Shigetoshi; Tsujimoto, Yoshimasa; Takashima, Ryokichi; Enoki, Yuki; Kato, Ikunoshin
PATENT ASSIGNEE(S): Takara Bio Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 386 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2002355079	A2	20021210	JP 2002-69354	20020313

PRIORITY APPLN. INFO.: JP 2001-73183 A 20010314
JP 2001-74993 A 20010315
JP 2001-102519 A 20010330

AB A **method** and kit for detecting endocrine-disrupting chems. using DNA microarrays are claimed. The **method** comprises preparing a nucleic acid sample containing mRNAs or cDNAs originating in cells, tissues, or organisms which have been brought into contact with a sample containing the endocrine disruptor. The nucleic acid sample is hybridized with DNA microarrays having genes affected by the endocrine disruptor or DNA fragments originating in these genes have been fixed. The results obtained are then compared with the results obtained with the control sample to select the gene affected by the endocrine disruptor. Genes whose expression is altered by tri-Bu tin, 4-octaphenol, 4-nonylphenol, di-N-Bu phthalate, dichlorohexyl phthalate, octachlorostyrene, benzophenone, diethylhexyl phthalate, diethylstilbestrol (DES), and 17-β estradiol (E2), were found in mice by DNA chip anal.

L13 ANSWER 10 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:907056 HCAPLUS
DOCUMENT NUMBER: 136:114324
TITLE: The **CtBP** family: Enigmatic and enzymatic **transcriptional** co-**repressors**
AUTHOR(S): Turner, Jeremy; Crossley, Merlin
CORPORATE SOURCE: Dept. of Biochemistry, University of Sydney, 2006, Australia
SOURCE: BioEssays (2001), 23(8), 683-690
CODEN: BIOEEJ; ISSN: 0265-9247
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. **Transcription factors** that associate with DNA sequences in promoters and enhancers often recruit co-**regulators** that modulate their activity. Many of these co-**regulators** have intrinsic enzymic activity and influence gene expression by modifying chromatin and altering its structure. Recently, a new family of co-**repressors**, the C-terminal binding proteins, has been described. These proteins recognize Pro-X-Asp-Leu-Ser (PXDLS) motifs in **DNA -binding proteins** and function as **transcriptional** co-**repressors** in **Drosophila**, Xenopus and mammals. The precise mechanisms by which they influence **transcription** are still under investigation. **CtBP**

proteins dimerize and can contact histone deacetylases; hence they may operate by linking deacetylases to DNA-bound **factors**. But it appears that **CtBP** proteins also have intrinsic enzymic activity. They have significant homol. to D-isomer-specific 2-hydroxy acid dehydrogenases, and remarkably one family member, rat **CtBP**, has been shown to have a second role, functioning as an acyl transferase in Golgi maintenance. These observations raise the possibility that **CtBP** proteins might **regulate** gene expression directly by means of their enzymic activities, in addition to serving as simple bridging proteins.

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 11 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:544336 HCAPLUS
DOCUMENT NUMBER: 135:224272
TITLE: Nuclear interpretation of Dpp signaling in **Drosophila**
AUTHOR(S): Affolter, Markus; Marty, Thomas; Vigano, M. Alessandra; Jazwinska, Anna
CORPORATE SOURCE: Abteilung Zellbiologie, Biozentrum der Universitat Basel, Basel, CH-4026, Switz.
SOURCE: EMBO Journal (2001), 20(13), 3298-3305
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 54 refs. Signaling by Decapentaplegic (Dpp), a member of the **TGFβ** superfamily of signaling mols. similar to vertebrate BMP2 and BMP4, has been implicated in many developmental **processes** in **Drosophila** melanogaster. Notably, Dpp acts as a long-range morphogen during imaginal disk growth and patterning. Genetic approaches led to the identification of a number of gene products that constitute the core signaling pathway. In addition to the ligand-activated heteromeric receptor complex and the signal-transducing intracellular **Smad proteins**, Dpp signaling requires two nuclear proteins, **Schnurri** (Shn) and Brinker (Brk), to prime cells for Dpp responsiveness. A complex interplay between the nuclear **factors** involved in Dpp signaling appears to control the **transcriptional** readout of the Dpp morphogen gradient. It remains to be seen whether similar mol. mechanisms operate in the nucleus in vertebrate systems.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 12 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:390191 HCAPLUS
DOCUMENT NUMBER: 136:97910
TITLE: **Transcriptional repression** by Suppressor of Hairless involves the binding of a Hairless-**dCtBP** complex in **Drosophila**
AUTHOR(S): Morel, V.; Lecourtois, M.; Massiani, O.; Maier, D.; Preiss, A.; Schweisguth, F.
CORPORATE SOURCE: Unite Mixte de Recherche 8544, Ecole Normale Superieure, Paris, 75230, Fr.
SOURCE: Current Biology (2001), 11(10), 789-792
CODEN: CUBLE2; ISSN: 0960-9822
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Notch is the receptor for a conserved signaling pathway that **regulates** numerous cell fate decisions during development [1]. Signal transduction involves the presenilin-dependent intracellular **processing** of Notch and the nuclear translocation of the intracellular domain of Notch, NICD [2-6]. NICD assocs. with Suppressor of Hairless [Su(H)], a **DNA binding protein**, and Mastermind (Mam), a **transcriptional** coactivator [7-9]. In the absence of Notch signaling, Su(H) acts as a **transcriptional repressor** [10, 11]. **Repression** by Su(H) is relieved by the activation of Notch [12-16]. In the **Drosophila** embryo, this **transcriptional** switch from **repression** to activation is important for patterning the expression of the single-minded (sim) gene along the dorsoventral axis [12]. Here, we investigate the mechanisms by which Su(H) inhibits the expression of Notch target genes in **Drosophila**. We show that Hairless, an antagonist of Notch signaling [17-19], is required to **repress** the **transcription** of the sim gene. Hairless forms a DNA-bound complex with Su(H). Furthermore, it directly binds the **Drosophila** C-terminal Binding Protein (**dCtBP**), which acts as a **transcriptional corepressor**. The **dCtBP** binding motif of Hairless is essential for the function of Hairless in vivo. We propose that Hairless mediates **transcriptional repression** by Su(H) via the recruitment of **dCtBP**.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 13 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:910882 HCAPLUS

DOCUMENT NUMBER: 134:174511

TITLE: The interaction of the carboxyl terminus-binding protein with the **Smad corepressor** TGIF is disrupted by a holoprosencephaly mutation in TGIF

AUTHOR(S): Melhuish, Tiffany A.; Wotton, David

CORPORATE SOURCE: Dep. Biochem. and Mol. Genet., Univ. Virginia, Charlottesville, VA, 22908, USA

SOURCE: Journal of Biological Chemistry (2000), 275(50), 39762-39766
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The homeodomain protein TGIF **represses transcription** in part by recruiting histone deacetylases. TGIF binds directly to DNA to **repress transcription** or interacts with **TGF-beta**.-activated Smads, thereby **repressing** genes normally activated by **TGF-β** . Loss of function mutations in TGIF result in holoprosencephaly (HPE) in humans. One HPE mutation in TGIF results in a single amino acid substitution in a conserved PLDLS motif within the amino-terminal **repression** domain. It is demonstrated that TGIF interacts with the **corepressor** carboxyl terminus-binding protein (**CtBP**) via this motif. **CtBP**, which was first identified by its ability to bind the adenovirus E1A protein, interacts both with gene-specific **transcriptional repressors** and with a subset of polycomb proteins. Efficient **repression** of **TGF-β** -activated gene responses by TGIF is dependent on interaction with **CtBP**, and TGIF is able to recruit **CtBP** to a **TGF-beta**.-activated Smad complex. Disruption of the PLDLS motif in TGIF abolishes

the interaction of **CtBP** with TGIF and compromises the ability of TGIF to **repress transcription**. Thus, at least one HPE mutation in TGIF appears to prevent **CtBP**-dependent **transcriptional repression** by TGIF, suggesting an important developmental role for the recruitment of **CtBP** by TGIF.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 14 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:748468 HCAPLUS
DOCUMENT NUMBER: 134:291025
TITLE: **Schnurri** mediates Dpp-dependent **repression** of brinker **transcription**
AUTHOR(S): Marty, Thomas; Muller, Bruno; Basler, Konrad; Affolter, Markus
CORPORATE SOURCE: Abteilung Zellbiologie, Biozentrum, Universitat Basel, Basel, CH-4056, Switz.
SOURCE: Nature Cell Biology (2000), 2(10), 745-749
CODEN: NCBIFN; ISSN: 1465-7392
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Signaling by Decapentaplegic (Dpp), a member of the **TGF**. **beta**. superfamily of signaling mols., controls many aspects of **Drosophila** development by activating and **repressing** target genes. Several essential components of the Dpp signaling pathway have been identified, including the Dpp receptors Punt and Thick veins (Tkv) as well as the cytoplasmic mediators **Mad** and **Medea** . For target genes to be activated, Dpp signaling must suppress **transcription** of a **repressor** encoded by the brinker (brk) gene. Here the authors show that **Schnurri** (Shn), a large zinc-finger protein, is essential for Dpp-mediated **repression** of brk **transcription**; in contrast, Shn is not required for target-gene activation. Thus, the Dpp signaling pathway bifurcates, downstream of the signal-mediating **SMAD proteins**, into a Shn-dependent pathway leading to brk **repression** and a Shn-independent pathway leading to gene activation. The existence of several Shn-like proteins in vertebrates and the observation that Brk functions in BMP signaling in Xenopus indicates that a similar **regulatory** cascade may be conserved in higher organisms.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 15 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:505206 HCAPLUS
DOCUMENT NUMBER: 133:233980
TITLE: **Schnurri** interacts with **Mad** in a Dpp-dependent manner
AUTHOR(S): Udagawa, Yoshiyuki; Hanai, Jun-Ichi; Tada, Kei-Ichiro; Grieder, Nicole C.; Momoeda, Mikio; Taketani, Yuji; Affolter, Markus; Kawabata, Masahiro; Miyazono, Kohei
CORPORATE SOURCE: Department of Biochemistry, The Cancer Institute of Japanese Foundation for Cancer Research (JFCR), Tokyo, 170-8455, Japan
SOURCE: Genes to Cells (2000), 5(5), 359-369
CODEN: GECEFL; ISSN: 1356-9597
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: Decapentaplegic (Dpp) is a member of the transforming growth **factor-β** superfamily. Dpp governs various developmental **processes** in **Drosophila** through the **transcriptional regulation** of a variety of genes. Signals of Dpp are transmitted from the cell membrane to the nucleus by **Medea** and **Mad**, both belonging to the **Smad protein** family. **Mad** was shown to bind to the Dpp-responsive element in genes such as vestigial, labial, and Ultrabithorax. The DNA binding affinity of **Smad proteins** is relatively low, and requires other nuclear **factor**(s) to form stable DNA binding complexes. **Schnurri** (shn) was identified as a candidate gene acting downstream of Dpp receptors, but its relevance to **Mad** has remained unknown. Results: We characterized the biochem. functions of Shn. Shn forms homo-oligomers. Shn is localized in the nucleus, and is likely to have multiple nuclear localizing signals. Finally, we found that Shn interacts with **Mad** in a Dpp-dependent manner. Conclusions: The present results argue that Shn may act as a nuclear component of the Dpp signaling pathway through direct interaction with **Mad**.
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 16 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:313229 HCAPLUS
DOCUMENT NUMBER: 133:69082
TITLE: **TGF-β** signaling from receptors to the nucleus
AUTHOR(S): Roberts, Anita B.
CORPORATE SOURCE: Laboratory of Cell Regulation and Carcinogenesis, National Cancer Institute, Bethesda, MD, 20892-5055, USA
SOURCE: Microbes and Infection (1999), 1(15), 1265-1273 CODEN: MCINFS; ISSN: 1286-4579
PUBLISHER: Editions Scientifiques et Medicales Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 64 refs. In the past three years, a novel signal transduction pathway downstream of the transforming growth **factor** -beta (**TGF-β**) superfamily receptor serine-threonine kinases has been shown to be mediated by a family of latent **transcription factors** called 'Smads'. These proteins mediate a short-circuited pathway in which a set of receptor-activated Smads are phosphorylated directly by the receptor kinase and then translocate to the nucleus complexed to the common mediator, Smad4, to participate in **transcriptional** complexes. Smads 2 and 3 mediate signals predominantly from the **TGF-beta**. receptors. Of these, specific roles have been ascribed to Smad3 in control of chemotaxis of neutrophils and macrophages and the inhibition of Smad3 activity by the oncogene **Evi-1** suggests that it may play a role in leukemogenesis. Other data, such as the induction by the inflammatory cytokine interferon-γ of an inhibitory Smad, Smad7, which blocks the actions of Smad3, suggest that identification of the specific gene targets of **Smad proteins** in immune cells will provide new insight into the mechanisms of **TGF-β** action on these cells.
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 17 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:467050 HCAPLUS

DOCUMENT NUMBER: 131:224366
TITLE: **SIP1**, a novel zinc finger/homeodomain repressor, interacts with **smad proteins** and binds to 5'-CACCT sequences in candidate target genes
AUTHOR(S): Verschueren, Kristin; Remacle, Jacques E.; Collart, Clara; Kraft, Harry; Baker, Betty S.; Tylzanowski, Przemko; Nelles, Luc; Wuytens, Gunther; Su, Ming-Tsan; Bodmer, Rolf; Smith, James C.; Huylebroeck, Danny
CORPORATE SOURCE: Department of Cell Growth, Differentiation and Development (VIB-07), Flanders Interuniversity Institute for Biotechnology (VIB), Louvain, B-3000, Belg.
SOURCE: Journal of Biological Chemistry (1999), 274(29), 20489-20498
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Activation of transforming growth **factor** β receptors causes the phosphorylation and nuclear translocation of **Smad proteins**, which then participate in the **regulation** of expression of target genes. We describe a novel Smad-interacting protein, **SIP1**, which was identified using the yeast two-hybrid system. Although **SIP1** interacts with the MH2 domain of receptor-**regulated** Smads in yeast and in vitro, its interaction with full-length Smads in mammalian cells requires receptor-mediated Smad activation. **SIP1** is a new member of the δEF1/Zfh-1 family of two-handed zinc finger/homeodomain proteins. Like δEF1, **SIP1** binds to 5'-CACCT sequences in different promoters, including the Xenopus brachyury promoter. Overexpression of either full-length **SIP1** or its C-terminal zinc finger cluster, which bind to the Xbra2 promoter in vitro, prevented expression of the endogenous Xbra gene in early Xenopus embryos. Therefore, **SIP1**, like δEF1, is likely to be a **transcriptional repressor**, which may be involved in the **regulation** of at least one immediate response gene for **activin**-dependent signal transduction pathways. The identification of this Smad-interacting protein opens new routes to investigate the mechanisms by which transforming growth **factor** β members exert their effects on expression of target genes in responsive cells and in the vertebrate embryo.
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 18 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:373541 HCAPLUS
DOCUMENT NUMBER: 131:166736
TITLE: **Transcriptional cofactors** of the FOG family interact with GATA proteins by means of multiple zinc fingers
AUTHOR(S): Fox, Archa H.; Liew, Chu; Holmes, Melissa; Kowalski, Kasper; Mackay, Joel; Crossley, Merlin
CORPORATE SOURCE: Department of Biochemistry, G08, University of Sydney, NSW, 2006, Australia
SOURCE: EMBO Journal (1999), 18(10), 2812-2822
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Friend of GATA-1 (FOG-1) is a zinc finger protein that has been shown to interact phys. with the erythroid **DNA-binding protein** GATA-1 and modulate its **transcriptional** activity. Recently, two new members of the FOG family have been identified: a mammalian protein, FOG-2, that also assocs. with GATA-1 and other mammalian GATA **factors**; and U-shaped, a **Drosophila** protein that interacts with the **Drosophila** GATA protein Pannier. FOG proteins contain multiple zinc fingers and it has been shown previously that the sixth finger of FOG-1 interacts specifically with the N-finger but not the C-finger of GATA-1. Here we show that fingers 1, 5 and 9 of FOG-1 also interact with the N-finger of GATA-1 and that FOG-2 and U-shaped also contain multiple GATA-interacting fingers. We define the key contact residues and show that these residues are highly conserved in GATA-interacting fingers. We examine the effect of selectively mutating the four interacting fingers of FOG-1 and show that each contributes to FOG-1's ability to modulate GATA-1 activity. Finally, we show that FOG-1 can **repress** GATA-1-mediated activation and present evidence that this ability involves the recently described **CtBP** co-**repressor** proteins that recognize all known FOG proteins.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 19 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:29423 HCAPLUS

DOCUMENT NUMBER: 130:192678

TITLE: **dCtBP** mediates **transcriptional repression** by Knirps, Kruppel and Snail in the **Drosophila** embryo

AUTHOR(S): Nibu, Yutaka; Zhang, Hailan; Bajor, Ewa; Barolo, Scott; Small, Stephen; Levine, Michael

CORPORATE SOURCE: Dep. Molecular and Cellular Biology, Division Genetics, University California, Berkeley, CA, 94720, USA

SOURCE: EMBO Journal (1998), 17(23), 7009-7020
CODEN: EMJODG; ISSN: 0261-4189

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The pre-cellular **Drosophila** embryo contains 10 well characterized sequence-specific **transcriptional repressors**, which **represent** a broad spectrum of **DNA-binding proteins**. Previous studies have shown that two of the **repressors**, Hairy and Dorsal, recruit a common co-**repressor** protein, Groucho. Here we present evidence that three different **repressors**, Knirps, Kruppel and Snail, recruit a different co-**repressor**, **dCtBP**. Mutant embryos containing diminished levels of material **dCtBP** products exhibit both segmentation and dorsoventral patterning defects, which can be attributed to loss of Kruppel, Knirps and Snail activity. In contrast, the Dorsal and Hairy **repressors** retain at least some activity in **dCtBP** mutant embryos. The **dCtBP** interacts with Kruppel, Knirps and Snail through a related sequence motif, PXDLSXK/H. This motif is essential for the **repression** activity of these proteins in transgenic embryos. We propose that **dCtBP represents** a major form of **transcriptional repression** in development, and that the Groucho and **dCtBP** co-**repressors** mediate sep. pathways of **repression**.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
=> d que stat l17
L1             3 SEA FILE=REGISTRY ABB=ON  ACTIVIN/CN
L2        233478 SEA FILE=HCAPLUS ABB=ON  ?TRANSCRIPT?(L)(?REPRES? OR ?FACTOR?
                 OR ?REGULAT?)
L3          4862 SEA FILE=HCAPLUS ABB=ON  L2 AND (?SMAD?(W)(?PROTEIN? OR
                 ?REPRESSOR?) OR DNA?(W)?BIND?(W)?PROTEIN?)
L4           847 SEA FILE=HCAPLUS ABB=ON  L3 AND (TGF-BETA OR L1 OR ?ACTIVIN?
                 OR ?DROSOPHILA?)
L9            19 SEA FILE=HCAPLUS ABB=ON  L4 AND (?CTBP? OR ?DCTBP? OR ?CTBP2?
                 OR EVI(W)1 OR ?GGIF? OR ?SIP1? OR ?SCHNURRI?)
L10            6 SEA FILE=HCAPLUS ABB=ON  L9 AND (MAD? OR ?MEDEA?)
L11           19 SEA FILE=HCAPLUS ABB=ON  L9 OR L10
L12            6 SEA FILE=HCAPLUS ABB=ON  L11 AND (?METHOD? OR ?TECHNIQ? OR
                 ?PROCES?)
L13           19 SEA FILE=HCAPLUS ABB=ON  L11 OR L12
L14          117 SEA L13
L15           81 DUP REMOV L14 (36 DUPLICATES REMOVED)
L17           30 SEA L15 AND TRANSFORM?(W) GROWTH?(W) FACTOR?

=> d ibib abs l17 1-30

L17  ANSWER 1 OF 30     MEDLINE on STN
ACCESSION NUMBER:   2004257634     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 15156182
TITLE:              Molecular mechanisms of leukemogenesis by AML1/EVI
                    -1.
AUTHOR:             Mitani Kinuko
CORPORATE SOURCE:   Department of Hematology, Dokkyo University School of
                    Medicine, Tochigi 321-0293, Japan.. kinukom-tky@umin.ac.jp
SOURCE:             Oncogene, (2004 May 24) 23 (24) 4263-9.  Ref: 28
                    Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY:       England: United Kingdom
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
                    General Review; (REVIEW)
                    (REVIEW, TUTORIAL)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200406
ENTRY DATE:         Entered STN: 20040525
                    Last Updated on STN: 20040616
                    Entered Medline: 20040615
AB   The AML1/EVI-1 chimeric gene is generated by the
     t(3;21)(q26;q22) translocation and plays a pivotal role in progression of
     hematopoietic stem cell malignancies such as chronic myelocytic leukemia
     and myelodysplastic syndrome.  In AML1/EVI-1, an
     N-terminal half of AML1 including a runt homology domain is fused to the
     entire zinc-finger EVI-1 protein.  AML1 is essential
     for hematopoietic cell development in fetal liver and its lineage-specific
     differentiation in adult.  In contrast, EVI-1 is
     barely expressed in normal hematopoietic cells, but it is overexpressed in
     chronic myelocytic leukemia in blastic crisis and myelodysplastic
     syndrome-derived leukemia.  There are at least four mechanisms identified
     in AML1/EVI-1 fusion protein that possibly lead into
     malignant transformation of hematopoietic stem cells.  Firstly, AML1/
     EVI-1 exerts dominant-negative effects over AML1-induced
     transcriptional activation.  Although target genes
     repressed by AML1/EVI-1 are still not known,
     binding competition to a specific DNA sequence and histone deacetylase
     recruitment through a co-repressor CtBP in EVI
     -1 part are conceivable underlying mechanisms for the
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dominant-negative effects. Secondly, AML1/**EVI-1** interferes with **TGF beta** signaling and antagonizes the growth-inhibitory effects of **TGF beta**. The first zinc-finger domain of **EVI-1** associates with Smad3, a **TGF beta** signal transducer, and **represses** its **transcriptional** activity by recruiting histone deacetylase through **CtBP** that interacts with **EVI-1**. Thirdly, AML1/**EVI-1** blocks JNK activity and prevents stress-induced apoptosis. AML1/**EVI-1** associates with JNK through the first zinc-finger domain of **EVI-1** and disturbs the association between JNK and its substrates. Lastly, AML1/**EVI-1** enhances AP-1 activity by activating the c-Fos promoter depending on the second zinc-finger domain of **EVI-1**, and promotes cell proliferation. All these functions cooperatively contribute to the malignant transformation of the hematopoietic stem cells by AML1/**EVI-1**.

L17 ANSWER 2 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2002418883 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12117808
TITLE: The role of **TGF beta** signaling in the formation of the dorsal nervous system is conserved between **Drosophila** and chordates.
AUTHOR: Rusten Tor Erik; Cantera Rafael; Kafatos Fotis C; Barrio Rosa
CORPORATE SOURCE: European Molecular Biology Laboratory, Meyerhofstrasse 1, D-69117 Heidelberg, Germany.
SOURCE: Development (Cambridge, England), (2002 Aug) 129 (15) 3575-84.
Journal code: 8701744. ISSN: 0950-1991.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20020814
Last Updated on STN: 20021002
Entered Medline: 20021001

AB **Transforming growth factor** beta signaling mediated by Decapentaplegic and Screw is known to be involved in defining the border of the ventral neurogenic region in the fruitfly. A second phase of Decapentaplegic signaling occurs in a broad dorsal ectodermal region. Here, we show that the dorsolateral peripheral nervous system forms within the region where this second phase of signaling occurs. Decapentaplegic activity is required for development of many of the dorsal and lateral peripheral nervous system neurons. Double mutant analysis of the Decapentaplegic signaling mediator **Schnurri** and the inhibitor Brinker indicates that formation of these neurons requires Decapentaplegic signaling, and their absence in the mutant is mediated by a counteracting repression by Brinker. Interestingly, the ventral peripheral neurons that form outside the Decapentaplegic signaling domain depend on Brinker to develop. The role of Decapentaplegic signaling on dorsal and lateral peripheral neurons is strikingly similar to the known role of **Transforming growth factor** beta signaling in specifying dorsal cell fates of the lateral (later dorsal) nervous system in chordates (Halocythia, zebrafish, Xenopus, chicken and mouse). It points to an evolutionarily conserved mechanism specifying dorsal cell fates in the nervous system of both protostomes and deuterostomes.

L17 ANSWER 3 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2002027770 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11451567
TITLE: **Transforming growth factor** beta signalling in vitro and in vivo: **activin** ligand-receptor interaction, Smad5 in vasculogenesis, and repression of target genes by the deltaEF1/ZEB-related **SIP1** in the vertebrate embryo.
AUTHOR: Zwijsen A; van Grunsven L A; Bosman E A; Collart C; Nelles L; Umans L; Van de Putte T; Wuytens G; Huylebroeck D; Verschueren K
CORPORATE SOURCE: Laboratory of Molecular Biology (Celgen), Department of Cell Growth, Differentiation and Development (VIB-07), Flanders Interuniversity Institute for Biotechnology (VIB), University of Leuven, Belgium.
SOURCE: Molecular and cellular endocrinology, (2001 Jun 30) 180 (1-2) 13-24. Ref: 88
Journal code: 7500844. ISSN: 0303-7207.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20020121
Last Updated on STN: 20020121
Entered Medline: 20011217

AB The identification and characterization of components of the **transforming growth factor** beta (TGFbeta) signalling pathway are proceeding at a very fast pace. To illustrate a number of our activities in this field, we first summarize our work aiming at the selection from a large collection of single residue substitution mutants of two **activin** A polypeptides in which D27 and K102, respectively, have been modified. This work has highlighted the importance of K102 and its positive charge for binding to **activin** type II receptors. **Activin** K102E, which did not bind to high-affinity receptor complexes, may be a valuable beta chain, when incorporated in recombinant inhibin to unambiguously detect novel inhibin binding sites at the cell surface. We then illustrate how Smad5 knockout mice and an overexpression approach with a truncated TGFbeta type II receptor in the mouse embryo can contribute to the identification of a novel TGFbeta-->TbetaRII/ALK1-->Smad5 pathway in endothelial cells in the embryo proper and the yolk sac vasculature. We conclude with a summary of our results with a Smad-interacting **transcriptional repressor** but focus on its biological significance in the vertebrate embryo.

L17 ANSWER 4 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2001611338 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11598015
TITLE: Brinker requires two corepressors for maximal and versatile repression in Dpp signalling.
AUTHOR: Hasson P; Muller B; Basler K; Paroush Z
CORPORATE SOURCE: Department of Biochemistry, The Hebrew University-Hadassah Medical School, PO Box 12272, Jerusalem 91120, Israel.
SOURCE: EMBO journal, (2001 Oct 15) 20 (20) 5725-36.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011105
Last Updated on STN: 20021022
Entered Medline: 20011205

AB decapentaplegic (dpp) encodes a **Drosophila transforming growth factor**-beta homologue that functions as a morphogen in the developing embryo and in adult appendage formation. In the wing imaginal disc, a Dpp gradient governs patterning along the anteroposterior axis by inducing regional expression of diverse genes in a concentration-dependent manner. Recent studies show that responses to graded Dpp activity also require an input from a complementary and opposing gradient of Brinker (Brk), a **transcriptional repressor** protein encoded by a Dpp target gene. Here we show that Brk harbours a functional and transferable **repression** domain, through which it recruits the **corepressors** Groucho and **CtBP**. By analysing **transcriptional** outcomes arising from the genetic removal of these **corepressors**, and by ectopically expressing Brk variants in the embryo, we demonstrate that these **corepressors** are alternatively used by Brk for **repressing** some Dpp-responsive genes, whereas for **repressing** other distinct target genes they are not required. Our results show that Brk utilizes multiple means to **repress** its endogenous target genes, allowing **repression** of a multitude of complex Dpp target promoters.

L17 ANSWER 5 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2001610640 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11668343
TITLE: Murine **Schnurri**-2 is required for positive selection of thymocytes.
COMMENT: Comment in: Nat Immunol. 2001 Nov;2(11):989-91. PubMed ID: 11685218
AUTHOR: Takagi T; Harada J; Ishii S
CORPORATE SOURCE: Laboratory of Molecular Genetics, RIKEN Tsukuba Institute, CREST Research Project of JST, 3-1-1 Koyadai, Tsukuba, Ibaraki 305-0074, Japan.
SOURCE: Nature immunology, (2001 Nov) 2 (11) 1048-53.
Journal code: 100941354. ISSN: 1529-2908.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011102
Last Updated on STN: 20020123
Entered Medline: 20011213

AB A key step in T cell development involves the positive selection of cells that recognize antigen presented by self-major histocompatibility complex. Yet, the signals that are activated by T cell receptor engagement and lead to cell survival remain unclear. We show here that mice lacking the **transcription factor Schnurri**-2 (Shn-2), a large metal-finger protein, had severely defective positive selection of CD4+ and CD8+ cells. **Drosophila** Shn acts as a **cofactor** of Smad homolog and is required for Decapentaplegic signaling. Vertebrates have at least three Shn orthologs (Shn-1, Shn-2 and Shn-3), which are thought to act as nuclear targets in the bone morphogenetic protein-**transforming growth factor**-beta-**activin** signaling pathways. These data raised the possibility

that the Smad-Shn-2 complex is involved in the thymic selection of T cells.

L17 ANSWER 6 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2001540678 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11587364
TITLE: Oncogenic mechanisms of **Evi-1** protein.
AUTHOR: Hirai H; Izutsu K; Kurokawa M; Mitani K
CORPORATE SOURCE: Department of Hematology and Oncology, Graduate School of Medicine, University of Tokyo, Hongo, Japan..
hhirai-tky@umin.ac.jp
SOURCE: Cancer chemotherapy and pharmacology, (2001 Aug) 48 Suppl 1 S35-40. Ref: 29
Journal code: 7806519. ISSN: 0344-5704.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011008
Last Updated on STN: 20011015
Entered Medline: 20011011

AB Although **Evi-1** is thought to promote growth or block differentiation in some cell types, its biological functions have not been elucidated. To explore the mechanisms underlying **Evi-1** -induced oncogenesis, we investigated whether **Evi-1** affects the signaling of **transforming growth factor** beta (**TGF-beta**), which inhibits proliferation of a wide range of cell types and is one of the most studied growth **regulatory factors**. We demonstrated that **Evi-1 represses TGF-beta** signaling and antagonizes its growth-inhibitory effects. Two separate regions of **Evi-1** are responsible for this **repression**, one of which is the first zinc-finger domain. Through this domain, **Evi-1** physically interacts with Smad3, an intracellular mediator of **TGF-beta** signaling, thereby suppressing the **transcriptional** activity of Smad3. These results define a novel function of **Evi-1** as a **repressor** of signaling components of **TGF-beta**. We also demonstrated that **Evi-1 represses** Smad-induced **transcriptional** activation by recruiting **CtBP** as a **corepressor**. **Evi-1** associates with **CtBP1** through one of the **CtBP**-binding consensus motifs within the region from amino acid 544 to 607, and this association is required for the efficient inhibition of **TGF-beta** signaling. A specific histone deacetylase (HDAc) inhibitor, trichostatin A (TSA), alleviates **Evi-1**-mediated **repression** of **TGF-beta** signaling, suggesting that HDAc is involved in **transcriptional repression** by **Evi-1**. This identifies a novel function of **Evi -1** as a member of **corepressor** complexes and suggests that aberrant recruitment of **corepressors** is one of the mechanisms involved in **Evi-1**-induced leukemogenesis. These results indicate that specific HDAc inhibitors may be useful in the treatment of **Evi-1**-induced neoplastic tumors, including myeloid leukemias.

L17 ANSWER 7 OF 30 MEDLINE on STN

ACCESSION NUMBER: 2001412880 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11432817
TITLE: Nuclear interpretation of Dpp signaling in **Drosophila**.
AUTHOR: Affolter M; Marty T; Vigano M A; Jazwinska A
CORPORATE SOURCE: Abteilung Zellbiologie, Biozentrum der Universitat Basel, Klingelbergstrasse 70, CH-4026 Basel, Switzerland.. Markus.Affolter@unibas.ch
SOURCE: EMBO journal, (2001 Jul 2) 20 (13) 3298-305. Ref: 52
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

AB Signaling by Decapentaplegic (Dpp), a member of the TGFbeta superfamily of signaling molecules similar to vertebrate BMP2 and BMP4, has been implicated in many developmental **processes** in **Drosophila** melanogaster. Notably, Dpp acts as a long-range morphogen during imaginal disc growth and patterning. Genetic approaches led to the identification of a number of gene products that constitute the core signaling pathway. In addition to the ligand-activated heteromeric receptor complex and the signal-transducing intracellular **Smad proteins**, Dpp signaling requires two nuclear proteins, **Schnurri** (Shn) and Brinker (Brk), to prime cells for Dpp responsiveness. A complex interplay between the nuclear **factors** involved in Dpp signaling appears to control the **transcriptional** readout of the Dpp morphogen gradient. It remains to be seen whether similar molecular mechanisms operate in the nucleus in vertebrate systems.

L17 ANSWER 8 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2001340867 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11313276
TITLE: The corepressor **CtBP** interacts with **Evi-1** to repress **transforming growth factor** beta signaling.
AUTHOR: Izutsu K; Kurokawa M; Imai Y; Maki K; Mitani K; Hirai H
CORPORATE SOURCE: Department of Hematology and Oncology, Graduate School of Medicine, University of Tokyo, Japan.
SOURCE: Blood, (2001 May 1) 97 (9) 2815-22.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010618
Last Updated on STN: 20010618
Entered Medline: 20010614

AB **Evi-1** is a zinc finger nuclear protein whose inappropriate expression leads to leukemic transformation of hematopoietic cells in mice and humans. This was previously shown to block the antiproliferative effect of **transforming growth factor** beta (**TGF-beta**). **Evi-1 represses TGF-beta** signaling by

direct interaction with Smad3 through its first zinc finger motif. Here, it is demonstrated that **Evi-1 represses** Smad-induced **transcription** by recruiting C-terminal binding protein (**CtBP**) as a **corepressor**. **Evi-1** associates with **CtBP1** through one of the consensus binding motifs, and this association is required for efficient inhibition of **TGF-beta** signaling. A specific inhibitor for histone deacetylase (HDAc) alleviates **Evi-1**-mediated **repression** of **TGF-beta** signaling, suggesting that HDAc is involved in the **transcriptional repression** by **Evi-1**. This identifies a novel function of **Evi-1** as a member of **corepressor** complexes and suggests that aberrant recruitment of **corepressors** is one of the mechanisms for **Evi-1**-induced leukemogenesis.

L17 ANSWER 9 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2001163762 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11263664
TITLE: **SIP1** (Smad interacting protein 1) and deltaEF1 (delta-crystallin enhancer binding **factor**) are structurally similar **transcriptional repressors.**
AUTHOR: van Grunsven L A; Schellens A; Huylebroeck D; Verschueren K
CORPORATE SOURCE: University of Leuven, Belgium.
SOURCE: Journal of bone and joint surgery. American volume, (2001) 83-A Suppl 1 (Pt 1) S40-7. Ref: 67
Journal code: 0014030. ISSN: 0021-9355.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20010425
Entered Medline: 20010419

AB BACKGROUND: **Smad proteins** are intracellular mediators of **transforming growth factor**-beta (TGFbeta) signalling that **regulate** gene expression by interacting with different classes of **transcription factors** including DNA-binding multi-zinc finger proteins. One of these, Smad interacting protein 1 (**SIP1**), is a novel two-handed zinc-finger protein that displays strong similarity with the **transcriptional repressor** delta-crystallin enhancer binding **factor** (deltaEF1). Here, we summarize what is known about the mechanism of action of both proteins and their role in vertebrate embryogenesis. Our data are discussed together with the present knowledge on other zinc-finger containing Smad interacting proteins. **METHODS**: The activities and function of **SIP1** have been analysed through documentation of expression patterns, the effect of over-expression of **SIP1** on target-gene expression, and promoter studies using Xenopus embryos. Moreover, S1P1/Smad complexes and their association with target promoter DNA were analyzed in biochemical studies. RESULTS: **SIP1** is a **transcriptional repressor** displaying overlapping DNA binding specificities with deltaEF1. An in vivo target of **SIP1** in Xenopus is a gene required for the formation of mesoderm, Brachyury (XBra). Our data indicate that **SIP1** is required to confine XBra gene expression to the mesoderm. Furthermore, the expression pattern in Xenopus invites us to speculate that **SIP1** plays a

role in specification/differentiation of neuroectoderm. Unlike deltaEF1, **SIP1** can bind directly to activated receptor **regulated** Smads (R-Smads) and recruit them to the DNA. This indicates that Smads may modulate the activity of **SIP1** as a **transcriptional repressor**. CONCLUSIONS: Our data point to a role of **SIP1** in developmental **processes regulated** by members of the TGFbeta family such as induction of mesoderm (mediated through **activin**-like signalling) and inhibition of neuroectoderm formation (mediated by bone morphogenetic proteins [BMPs]). Whereas **SIP1** could act in TGFbeta signal transduction by virtue of interaction with activated R-Smads, genetic studies in the mouse indicate that deltaEF1 may act in certain TGFbeta pathways-i.e., BMPs and growth and differentiation **factors** (GDFs)-as well. The molecular mechanisms by which these **transcriptional repressors** act, as well as the function of the **SIP1**/Smad interaction, remain to be elucidated. Clinical Relevance: Mutations in components of the TGFbeta signalling pathways have been associated with disease and congenital malformations. We anticipate that identification of Smad interacting **transcription factors** including **SIP1** and their targets will help us to understand the molecular basis of certain pathologies.

L17 ANSWER 10 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2001106053 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10995736
TITLE: The interaction of the carboxyl terminus-binding protein with the **Smad corepressor** TGIF is disrupted by a holoprosencephaly mutation in TGIF.
AUTHOR: Melhuish T A; Wotton D
CORPORATE SOURCE: Department of Biochemistry and Molecular Genetics and Center for Cell Signaling, University of Virginia, Charlottesville, Virginia 22908, USA.
SOURCE: Journal of biological chemistry, (2000 Dec 15) 275 (50) 39762-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010208

AB The homeodomain protein TGIF **represses transcription** in part by recruiting histone deacetylases. TGIF binds directly to DNA to **repress transcription** or interacts with **TGF-beta**-activated Smads, thereby **repressing** genes normally activated by **TGF-beta**. Loss of function mutations in TGIF result in holoprosencephaly (HPE) in humans. One HPE mutation in TGIF results in a single amino acid substitution in a conserved PLDLS motif within the amino-terminal **repression** domain. We demonstrate that TGIF interacts with the **corepressor** carboxyl terminus-binding protein (**CtBP**) via this motif. **CtBP**, which was first identified by its ability to bind the adenovirus E1A protein, interacts both with gene-specific **transcriptional repressors** and with a subset of polycomb proteins. Efficient **repression** of **TGF-beta**-activated gene responses by TGIF is dependent on interaction with **CtBP**, and we show that TGIF is able to recruit **CtBP** to a **TGF-beta**-activated Smad complex. Disruption of the PLDLS motif in TGIF abolishes the interaction of **CtBP** with TGIF and compromises

the ability of TGIF to **repress transcription**. Thus, at least one HPE mutation in TGIF appears to prevent **CtBP** -dependent **transcriptional repression** by TGIF, suggesting an important developmental role for the recruitment of **CtBP** by TGIF.

L17 ANSWER 11 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2001055858 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11025666
TITLE: **Schnurri** mediates Dpp-dependent **repression** of brinker **transcription**.
AUTHOR: Marty T; Muller B; Basler K; Affolter M
CORPORATE SOURCE: Abteilung Zellbiologie, Biozentrum, Universitat Basel, Klingelbergstrasse 70, CH-4056 Basel, Switzerland.
SOURCE: Nature cell biology, (2000 Oct) 2 (10) 745-9. Journal code: 100890575. ISSN: 1465-7392.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001219

AB Signalling by Decapentaplegic (Dpp), a member of the TGFbeta superfamily of signalling molecules, controls many aspects of **Drosophila** development by activating and **repressing** target genes. Several essential components of the Dpp signalling pathway have been identified, including the Dpp receptors Punt and Thick veins (Tkv) as well as the cytoplasmic mediators **Mad** and **Medea**. For target genes to be activated, Dpp signalling must suppress **transcription** of a **repressor** encoded by the brinker (brk) gene. Here we show that **Schnurri** (Shn), a large zinc-finger protein, is essential for Dpp-mediated **repression** of brk **transcription**; in contrast, Shn is not required for target-gene activation. Thus, the Dpp signalling pathway bifurcates, downstream of the signal-mediating **SMAD proteins**, into a Shn-dependent pathway leading to brk **repression** and a Shn-independent pathway leading to gene activation. The existence of several Shn-like proteins in vertebrates and the observation that Brk functions in BMP signalling in Xenopus indicates that a similar **regulatory** cascade may be conserved in higher organisms.

L17 ANSWER 12 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2000385480 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10886364
TITLE: **Schnurri** interacts with **Mad** in a Dpp-dependent manner.
AUTHOR: Udagawa Y; Hanai J; Tada K; Grieder N C; Momoeda M; Taketani Y; Affolter M; Kawabata M; Miyazono K
CORPORATE SOURCE: Department of Biochemistry, The Cancer Institute of Japanese Foundation for Cancer Research (JFCR), 1-37-1 Kami-ikebukuro, Toshima-ku, Tokyo 170-8455, Japan.
SOURCE: Genes to cells : devoted to molecular & cellular mechanisms, (2000 May) 5 (5) 359-69. Journal code: 9607379. ISSN: 1356-9597.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000818
Last Updated on STN: 20000818
Entered Medline: 20000808

AB BACKGROUND: Decapentaplegic (Dpp) is a member of the **transforming growth factor**-beta superfamily. Dpp governs various developmental **processes** in **Drosophila** through the **transcriptional regulation** of a variety of genes. Signals of Dpp are transmitted from the cell membrane to the nucleus by **Medea** and **Mad**, both belonging to the **Smad protein** family. **Mad** was shown to bind to the Dpp-responsive element in genes such as vestigial, labial, and Ultrabithorax. The DNA binding affinity of **Smad proteins** is relatively low, and requires other nuclear **factor**(s) to form stable DNA binding complexes. **schnurri** (shn) was identified as a candidate gene acting downstream of Dpp receptors, but its relevance to **Mad** has remained unknown. RESULTS: We characterized the biochemical functions of Shn. Shn forms homo-oligomers. Shn is localized in the nucleus, and is likely to have multiple nuclear localizing signals. Finally, we found that Shn interacts with **Mad** in a Dpp-dependent manner. CONCLUSIONS: The present results argue that Shn may act as a nuclear component of the Dpp signalling pathway through direct interaction with **Mad**.

L17 ANSWER 13 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2000079452 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10611754
TITLE: **TGF-beta** signaling from receptors to the nucleus.
AUTHOR: Roberts A B
CORPORATE SOURCE: Laboratory of Cell Regulation and Carcinogenesis, National Cancer Institute Building 41, Room C629, 41 Library Drive, MSC 5055, Bethesda, MD 20892-5055, USA.
SOURCE: Microbes and infection / Institut Pasteur, (1999 Dec) 1 (15) 1265-73. Ref: 64
Journal code: 100883508. ISSN: 1286-4579.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000309
Last Updated on STN: 20000309
Entered Medline: 20000223

AB In the past three years, a novel signal transduction pathway downstream of the **transforming growth factor**-beta (**TGF-beta**) superfamily receptor serine-threonine kinases has been shown to be mediated by a family of latent **transcription factors** called 'Smads'. These proteins mediate a short-circuited pathway in which a set of receptor-activated Smads are phosphorylated directly by the receptor kinase and then translocate to the nucleus complexed to the common mediator, Smad4, to participate in **transcriptional** complexes. Smads 2 and 3 mediate signals predominantly from the **TGF-beta** receptors. Of these, specific roles have been ascribed to Smad3 in control of chemotaxis of neutrophils and macrophages and the inhibition of Smad3 activity by the oncogene **Evi-1** suggests that it may play a role in leukemogenesis. Other data, such as the induction by the inflammatory

cytokine interferon-gamma of an inhibitory Smad, Smad7, which blocks the actions of Smad3, suggest that identification of the specific gene targets of **Smad proteins** in immune cells will provide new insight into the mechanisms of **TGF-beta** action on these cells.

L17 ANSWER 14 OF 30 MEDLINE on STN
ACCESSION NUMBER: 1999440737 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10512186
TITLE: The role of **transcription factors** involved in TGFbeta superfamily signaling during development.
AUTHOR: Watanabe M; Whitman M
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston, MA 02115, USA.. mwatanbe@hms.harvard.edu
SOURCE: Cellular and molecular biology (Noisy-le-Grand, France), (1999 Jul) 45 (5) 537-43. Ref: 56
Journal code: 9216789. ISSN: 0145-5680.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000124

AB Recent studies of **transforming growth factor** -beta (**TGF-beta**) signaling have identified a signaling pathway that includes Ser/Thr kinase transmembrane receptors, intracellular substrates and transducers of receptor activation known as Smads, and DNA-binding **transcription factors** that are **regulated** by interaction with Smads. Both genetic and biochemical studies show that Smads are central mediators of **TGF-beta** signaling. How do Smads **regulate** the expression of target genes in the nucleus? Over the past three years, **transcription factors** involved in **TGF-beta** signaling have been identified and the molecular events in the nucleus have begun to be understood. Both Smads, which have intrinsic DNA binding activity, and additional **transcription factors**, act together to **regulate** the expression of target genes in the nucleus. Smads are relatively ubiquitously expressed in embryos during the development, while interacting **transcription factors** are expressed with a restricted pattern, either temporally or spatially. Therefore the developmental specificity of **TGF-beta** signaling may be, at least in part, determined by cell-type specific **transcription factors**.

L17 ANSWER 15 OF 30 MEDLINE on STN
ACCESSION NUMBER: 1999329065 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10400677
TITLE: **SIP1**, a novel zinc finger/homeodomain repressor, interacts with **Smad proteins** and binds to 5'-CACCT sequences in candidate target genes.
AUTHOR: Verschueren K; Remacle J E; Collart C; Kraft H; Baker B S; Tylzanowski P; Nelles L; Wuytens G; Su M T; Bodmer R; Smith J C; Huylebroeck D
CORPORATE SOURCE: Department of Cell Growth, Differentiation and Development (VIB-07), Flanders Interuniversity Institute for

Biotechnology (VIB), Herestraat49, B-3000 Leuven, Belgium.
SOURCE: Journal of biological chemistry, (1999 Jul 16) 274 (29) 20489-98.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF033116
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990827
Last Updated on STN: 19990827
Entered Medline: 19990819

AB Activation of **transforming growth factor** beta receptors causes the phosphorylation and nuclear translocation of **Smad proteins**, which then participate in the **regulation** of expression of target genes. We describe a novel Smad-interacting protein, **SIP1**, which was identified using the yeast two-hybrid system. Although **SIP1** interacts with the MH2 domain of receptor-**regulated** Smads in yeast and in vitro, its interaction with full-length Smads in mammalian cells requires receptor-mediated Smad activation. **SIP1** is a new member of the deltaEF1/Zfh-1 family of two-handed zinc finger/homeodomain proteins. Like deltaEF1, **SIP1** binds to 5'-CACCT sequences in different promoters, including the Xenopus brachyury promoter. Overexpression of either full-length **SIP1** or its C-terminal zinc finger cluster, which bind to the Xbra2 promoter in vitro, prevented expression of the endogenous Xbra gene in early Xenopus embryos. Therefore, **SIP1**, like deltaEF1, is likely to be a **transcriptional repressor**, which may be involved in the **regulation** of at least one immediate response gene for **activin**-dependent signal transduction pathways. The identification of this Smad-interacting protein opens new routes to investigate the mechanisms by which **transforming growth factor** beta members exert their effects on expression of target genes in responsive cells and in the vertebrate embryo.

L17 ANSWER 16 OF 30 MEDLINE on STN
ACCESSION NUMBER: 1999055516 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9834202
TITLE: The t(3;21) fusion product, AML1/**Evi-1**, interacts with Smad3 and blocks **transforming growth factor**-beta-mediated growth inhibition of myeloid cells.
AUTHOR: Kurokawa M; Mitani K; Imai Y; Ogawa S; Yazaki Y; Hirai H
CORPORATE SOURCE: Department of Hematology & Oncology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan.
SOURCE: Blood, (1998 Dec 1) 92 (11) 4003-12.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19990105

AB The t(3;21)(q26;q22) chromosomal translocation associated with blastic crisis of chronic myelogenous leukemia results in the formation of the AML1/**Evi-1** chimeric protein, which is thought to play

a causative role in leukemic transformation of hematopoietic cells. Here we show that AML1/**Evi-1** represses growth-inhibitory signaling by **transforming growth factor**-beta (**TGF-beta**) in 32Dcl3 myeloid cells. The activity of AML1/**Evi-1** to repress **TGF-beta** signaling depends on the two separate regions of the **Evi-1** portion, one of which is the first zinc finger domain. AML1/**Evi-1** interacts with Smad3, an intracellular mediator of **TGF-beta** signaling, through the first zinc finger domain, and represses the Smad3 activity, as **Evi-1** does. We also show that suppression of endogenous **Evi-1** in leukemic cells carrying inv(3) restores **TGF-beta** responsiveness. Taken together, AML1/**Evi-1** acts as an inhibitor of **TGF-beta** signaling by interfering with Smad3 through the **Evi-1** portion, and both AML1/**Evi-1** and **Evi-1** repress **TGF-beta**-mediated growth suppression in hematopoietic cells. Thus, AML1/**Evi-1** may contribute to leukemogenesis by specifically blocking growth-inhibitory signaling of **TGF-beta** in the t(3;21) leukemia.

L17 ANSWER 17 OF 30 MEDLINE on STN
ACCESSION NUMBER: 1998328072 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9665135
TITLE: The oncoprotein **Evi-1** represses **TGF-beta** signalling by inhibiting Smad3.
AUTHOR: Kurokawa M; Mitani K; Irie K; Matsuyama T; Takahashi T; Chiba S; Yazaki Y; Matsumoto K; Hirai H
CORPORATE SOURCE: The Third Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Japan.
SOURCE: Nature, (1998 Jul 2) 394 (6688) 92-6.
Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980731
Last Updated on STN: 19980731
Entered Medline: 19980720

AB **Evi-1** encodes a zinc-finger protein that may be involved in leukaemic transformation of haematopoietic cells. **Evi-1** has two zinc-finger domains, one with seven repeats of a zinc-finger motif and one with three repeats, and it has characteristics of a **transcriptional regulator**. Although **Evi-1** is thought to be able to promote growth and to block differentiation in some cell types, its biological functions are poorly understood. Here we study the mechanisms that underlie oncogenesis induced by **Evi-1** by investigating whether **Evi-1** perturbs signalling through **transforming growth factor**-beta (**TGF-beta**), one of the most studied growth-**regulatory factors**, which inhibits proliferation of a wide range of cell types. We show that **Evi-1 represses TGF-beta** signalling and antagonizes the growth-inhibitory effects of **TGF-beta**. Two separate regions of **Evi-1** are responsible for this **repression**; one of these regions is the first zinc-finger domain. Through this domain, **Evi-1** interacts with Smad3, an intracellular mediator of **TGF-beta** signalling, thereby suppressing the **transcriptional**

activity of Smad3. These results define a new function of **Evi-1** as a **repressor** of signalling through **TGF-beta**.

L17 ANSWER 18 OF 30 MEDLINE on STN
ACCESSION NUMBER: 1998190064 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9521913
TITLE: A genetic screen for modifiers of **Drosophila** decapentaplegic signaling identifies mutations in punt, Mothers against dpp and the BMP-7 homologue, 60A.
AUTHOR: Chen Y; Riese M J; Killinger M A; Hoffmann F M
CORPORATE SOURCE: McArdle Laboratory for Cancer Research, Medical School, University of Wisconsin-Madison, Madison, Wisconsin 53706, USA.
CONTRACT NUMBER: CA07175 (NCI)
SOURCE: Development (Cambridge, England), (1998 May) 125 (9) 1759-68.
Journal code: 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980716
Last Updated on STN: 20020420
Entered Medline: 19980702

AB decapentaplegic (dpp) is a **Transforming Growth Factor** beta (**TGF-beta**)-related growth factor that controls multiple developmental **processes** in **Drosophila**. To identify components involved in dpp signaling, we carried out a genetic screen for dominant enhancer mutations of a hypomorphic allele of thick veins (tkv), a type I receptor for dpp. We recovered new alleles of tkv, punt, Mothers against dpp (**Mad**) and **Medea** (Med), all of which are known to mediate dpp signaling. We also recovered mutations in the 60A gene which encodes another **TGF-beta**-related factor in **Drosophila**. DNA sequence analysis established that all three 60A alleles were nonsense mutations in the prodomain of the 60A polypeptide. These mutations in 60A caused defects in midgut morphogenesis and fat body differentiation. We present evidence that when dpp signaling is compromised, lowering the level of 60A impairs several dpp-dependent developmental **processes** examined, including the patterning of the visceral mesoderm, the embryonic ectoderm and the imaginal discs. These results provide the first in vivo evidence for the involvement of 60A in the dpp pathway. We propose that 60A activity is required to maintain optimal signaling capacity of the dpp pathway, possibly by forming biologically active heterodimers with Dpp proteins.

L17 ANSWER 19 OF 30 MEDLINE on STN
ACCESSION NUMBER: 1998043873 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9334286
TITLE: punt and **schnurri** regulate a somatically derived signal that restricts proliferation of committed progenitors in the germline.
AUTHOR: Matunis E; Tran J; Gonczy P; Caldwell K; DiNardo S
CORPORATE SOURCE: The Rockefeller University, NYC, NY 10021-6399, USA.
CONTRACT NUMBER: GM16991 (NIGMS)
SOURCE: Development (Cambridge, England), (1997 Nov) 124 (21) 4383-91.
Journal code: 8701744. ISSN: 0950-1991.

PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971217

AB To identify regulators of stem cell lineages, we are focusing on spermatogenesis in **Drosophila**. In spermatogenesis, each germline stem cell divides asymmetrically, renewing itself and producing a transiently amplifying daughter, which divides four times. By screening for mutants in which daughter cells fail to stop dividing, we find that the **TGF-beta** signal transducers **schnurri** and punt are required to limit transient amplification of germ cells. Mosaic analysis demonstrates that punt and **schnurri** act within somatic cyst cells that surround germ cells, rather than in germ cells. Thus, a cyst-cell-derived signal restricts germ cell proliferation and this signal is initiated by input from a member of the **TGF-beta** superfamily. Thus, a signal relay regulates progression through the germline stem cell lineage.

L17 ANSWER 20 OF 30 MEDLINE on STN
ACCESSION NUMBER: 97175397 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9023056
TITLE: Signal transduction by members of the **transforming growth factor**-beta superfamily.
AUTHOR: Attisano L; Wrana J L
CORPORATE SOURCE: Department of Anatomy and Cell Biology, University of Toronto, Ontario, Canada.. lattis@sickkids.on.ca
SOURCE: Cytokine & growth factor reviews, (1996 Dec) 7 (4) 327-39. Ref: 127
Journal code: 9612306. ISSN: 1359-6101.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970507
Last Updated on STN: 20021022
Entered Medline: 19970428

AB **Transforming growth factor**-beta (**TGF beta**) superfamily members exert their diverse biological effects through their interaction with heteromeric receptor complexes of transmembrane serine/threonine kinases. Both components of the receptor complex, known as receptor I and receptor II are essential for signal transduction. The composition of these complexes can vary significantly due to the promiscuous nature of the ligands and the receptors, and this diversity of interactions can yield a variety of biological responses. Several receptor interacting proteins and potential mediators of signal transduction have now been identified. Recent advances, particularly in our understanding of the function of Mothers against dpp-related (**MADR**) proteins, are providing new insights into how the **TGF beta** superfamily signals its diverse biological activities.

L17 ANSWER 21 OF 30 MEDLINE on STN
ACCESSION NUMBER: 97165272 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9115845
TITLE: Signalling to the nucleus by members of the **transforming growth factor**-beta (**TGF-beta**) superfamily.
AUTHOR: Hill C S
CORPORATE SOURCE: Ludwig Institute For Cancer Research, London, UK.
SOURCE: Cellular signalling, (1996 Dec) 8 (8) 533-44. Ref: 125
Journal code: 8904683. ISSN: 0898-6568.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970506
Last Updated on STN: 20000303
Entered Medline: 19970421

L17 ANSWER 22 OF 30 MEDLINE on STN
ACCESSION NUMBER: 96280886 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8702186
TITLE: BMP signaling in **Drosophila** embryogenesis.
AUTHOR: Arora K; O'Connor M B; Warrior R
CORPORATE SOURCE: Department of Developmental and Cell Biology, University of California, Irvine 92717, USA.
SOURCE: Annals of the New York Academy of Sciences, (1996 Jun 8) 785 80-97. Ref: 68
Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960912
Last Updated on STN: 20021022
Entered Medline: 19960903

L17 ANSWER 23 OF 30 MEDLINE on STN
ACCESSION NUMBER: 96017650 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7588072
TITLE: A **Drosophila** protein related to the human zinc finger **transcription factor** PRDII/MBPI/HIV-EP1 is required for dpp signaling.
AUTHOR: Staehling-Hampton K; Laughon A S; Hoffmann F M
CORPORATE SOURCE: McArdle Laboratory for Cancer Research, University of Wisconsin Medical School, Madison 53706, USA.
CONTRACT NUMBER: CA07175 (NCI)
CA09135 (NCI)
RR06610 (NCRR)
SOURCE: Development (Cambridge, England), (1995 Oct) 121 (10) 3393-403.
Journal code: 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U31368

ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951130

AB Little is known about the signal transduction pathways by which cells respond to mammalian **TGF-beta** s or to decapentaplegic (dpp), a **Drosophila TGF-beta**-related **factor**. Here we describe the genetic and molecular characterization of **Drosophila schnurri** (shn), a putative **transcription factor** implicated in dpp signaling. The shn protein has eight zinc fingers and is related to a human **transcription factor**, PRDII/MBPI/HIV-EP1, that binds to nuclear **factor**-kappa B-binding sites and activates **transcription** from the HIV long terminal repeat (LTR). shn mRNA is expressed in a dynamic pattern in the embryo that includes most of the known target tissues of dpp, including the dorsal blastoderm, the mesodermal germlayer and parasegments 4 and 7 of the midgut. Mutations in shn affect several developmental **processes regulated** by dpp including induction of visceral mesoderm cell fate, dorsal/ventral patterning of the lateral ectoderm and wing vein formation. Absence of shn function blocks the expanded expression of the homeodomain protein bagpipe in the embryonic mesoderm caused by ectopic dpp expression, illustrating a requirement for shn function downstream of dpp action. We conclude that shn function is critical for cells to respond properly to dpp and propose that shn protein is the first identified downstream component of the signal transduction pathway used by dpp and its receptors.

L17 ANSWER 24 OF 30 MEDLINE on STN
ACCESSION NUMBER: 95292345 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7774017
TITLE: The **Drosophila schnurri** gene acts in the Dpp/**TGF beta** signaling pathway and encodes a **transcription factor** homologous to the human MBP family.
AUTHOR: Arora K; Dai H; Kazuko S G; Jamal J; O'Connor M B; Letsou A; Warrior R
CORPORATE SOURCE: Department of Molecular Biology and Biochemistry, University of California, Irvine 92717, USA.
CONTRACT NUMBER: GM 00599 (NIGMS)
GM 47462 (NIGMS)
GM48659 (NIGMS)
SOURCE: Cell, (1995 Jun 2) 81 (5) 781-90.
Journal code: 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U31368
ENTRY MONTH: 199507
ENTRY DATE: Entered STN: 19950720
Last Updated on STN: 19950720
Entered Medline: 19950713

AB Decapentaplegic (dpp), a **TGF beta**-related ligand, plays a key role in **Drosophila** development. Although dpp receptors have been isolated, the downstream components of the signaling pathway remain to be identified. We have cloned the **schnurri** (shn) gene and show that it encodes a putative zinc finger **transcription factor** homologous to the human major histocompatibility complex-binding proteins 1 and 2. Mutations in shn

affect multiple events that require dpp signaling as well as the **transcription** of dpp-responsive genes. Genetic interactions and the strikingly similar phenotypes of mutations in shn and the dpp receptors encoded by thick veins and punt suggest that shn plays a downstream role in dpp signaling.

L17 ANSWER 25 OF 30 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:312420 BIOSIS
DOCUMENT NUMBER: PREV200300312420
TITLE: Opposing functions of ZEB proteins in the regulation of the TGFbeta/BMP signaling pathway.
AUTHOR(S): Postigo, Antonio A. [Reprint Author]
CORPORATE SOURCE: Division of Molecular Oncology, Department of Internal Medicine, Washington University School of Medicine, Saint Louis, MO, 63110, USA
apostigo@im.wustl.edu
SOURCE: EMBO (European Molecular Biology Organization) Journal, (May 15 2003) Vol. 22, No. 10, pp. 2443-2452. print.
ISSN: 0261-4189 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jul 2003
Last Updated on STN: 2 Jul 2003
AB Binding of TGFbeta/BMP **factors** to their receptors leads to translocation of **Smad proteins** to the nucleus where they activate **transcription** of target genes. The two-handed zinc finger proteins encoded by Zfhx1a and Zfhx1b, ZEB-1/deltaEF1 and ZEB-2/**SIP1**, respectively, **regulate** gene expression and differentiation programs in a number of tissues. Here I demonstrate that ZEB proteins are also crucial **regulators** of TGFbeta/BMP signaling with opposing effects on this pathway. Both ZEB proteins bind to Smads, but while ZEB-1/deltaEF1 synergizes with **Smad proteins** to activate **transcription**, promote osteoblastic differentiation and induce cell growth arrest, the highly related ZEB-2/**SIP1** protein has the opposite effect. Finally, the ability of TGFbeta to mediate **transcription** of TGFbeta-dependent genes and induce growth arrest depends on the presence of endogenous ZEB-1/deltaEF1 protein.

L17 ANSWER 26 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003457732 EMBASE
TITLE: TGIF2 Interacts with Histone Deacetylase I and **Represses Transcription.**
AUTHOR: Melhuish T.A.; Gallo C.M.; Wotton D.
CORPORATE SOURCE: D. Wotton, Center for Cell Signaling, University of Virginia, Hospital West, Charlottesville, VA 22908, United States. dw2p@virginia.edu
SOURCE: Journal of Biological Chemistry, (24 Aug 2001) 276/34 (32109-32114).
Refs: 49
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB TG-interacting **factor** (TGIF) is a **transcriptional repressor**, which **represses transcription** by

binding directly to DNA or interacts with **transforming growth factor** α (**TGF.beta** .)-activated Smads, thereby **repressing TGF.beta.**-responsive gene expression. Mutation of TGIF in humans causes holoprosencephaly, a severe genetic disorder affecting craniofacial development. Searching human expressed sequence tag data bases revealed the presence of clones encoding a TGIF-related protein (TGIF2), which contains two regions of high sequence identity with TGIF. Here we show that, like TGIF, TGIF2 recruits histone deacetylase, but in contrast to TGIF, is unable to interact with the **corepressor CtBP**. TGIF2 and TGIF have very similar DNA-binding homeodomains, and TGIF2 **represses transcription** when bound to DNA via a TGIF binding site. TGIF2 interacts with **TGF**β -activated Smads and **represses TGF**β -responsive **transcription.** TGIF2 appears to be a context-independent **transcriptional repressor,** which can perform similar functions to TGIF and may play a role in **processes,** which, when disrupted by mutations in TGIF, cause holoprosencephaly.

L17 ANSWER 27 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003393221 EMBASE
TITLE: **Transforming growth factor** -β signaling in normal and malignant hematopoiesis.
AUTHOR: Kim S.-J.; Lettirio J.
CORPORATE SOURCE: Dr. S.-J. Kim, Lab. Cell Regulation/Carcinogenesis, National Cancer Institute, 41 Library Drive, Bethesda, MD 20892-5055, United States
SOURCE: Leukemia, (1 Sep 2003) 17/9 (1731-1737).
Refs: 106
ISSN: 0887-6924 CODEN: LEUKED
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
022 Human Genetics
025 Hematology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Transforming growth factor**-β (**TGF**-β) is perhaps the most potent endogenous negative **regulator** of hematopoiesis. The intracellular signaling events mediating the effects of **TGF**-β are multiple, involving extensive crosstalk between Smad-dependent and MAP-kinase-dependent pathways. We are only beginning to understand the importance of the balance between these cascades as a determinant of the response to **TGF**-β , and have yet to determine the roles that disruption in **TGF**-β signaling pathways might play in leukemogenesis. This review summarizes current knowledge regarding the function of **TGF**-β in normal and malignant hematopoiesis. The principal observations **made** by gene targeting studies in mice are reviewed, with an emphasis on how a disruption of this pathway in vivo can affect blood cell development and immune homeostasis. We overview genetic alterations that lead to impaired **TGF**-β signaling in hematopoietic neoplasms, including the suppression of Smad-dependent **transcriptional** responses by oncoproteins such as Tax and **Evi-1,** and fusion proteins such as AML1/ETO. We also consider mutations in genes encoding components of the core cell cycle machinery, such as p27(Kip1)

and p15(INK4A), and emphasize their impact on the ability of **TGF**-β to induce G1 arrest. The implications of these observations are discussed, and opinions regarding important directions for future research on **TGF-β** in hematopoiesis are provided.

L17 ANSWER 28 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001407503 EMBASE
TITLE: Positive selection in a **Schnurri**.
AUTHOR: Gascoigne N.R.J.
CORPORATE SOURCE: N.R.J. Gascoigne, Department of Immunology, IMMI, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, United States. gascoigne@scripps.edu
SOURCE: Nature Immunology, (2001) 2/11 (989-991).
Refs: 11
ISSN: 1529-2908 CODEN: NIAMCZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
LANGUAGE: English

L17 ANSWER 29 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001122537 EMBASE
TITLE: **SIP1** (smad interacting protein 1) and δEF1 (δ-crystallin enhancer binding **factor**) are structurally similar **transcriptional repressors**. A current survey of their functions and mechanisms of action in **transforming growth factor-β** signalling.
AUTHOR: Van Grunsven L.A.; Schellens A.; Huylebroeck D.; Verschueren K.
CORPORATE SOURCE: Dr. L.A. Van Grunsven, Laboratory of Molecular Biology, KULeuven, Herestraat 49, Leuven, Belgium. kristin@med.kuleuven.ac.be
SOURCE: Journal of Bone and Joint Surgery - Series A, (2001) 83/SUPPL. 1 (S140-S147).
Refs: 67
ISSN: 0021-9355 CODEN: JBJSA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 021 Developmental Biology and Teratology
029 Clinical Biochemistry
033 Orthopedic Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background: **Smad proteins** are intracellular mediators of **transforming growth factor**-β (**TGF**β) signalling that **regulate** gene expression by interacting with different classes of **transcription factors** including DNA-binding multi-zinc finger proteins. One of these, Smad interacting protein 1 (**SIP1**), is a novel two-handed zinc-finger protein that displays strong similarity with the **transcriptional repressor** δ-crystallin enhancer binding **factor** (δEF1). Here, we summarize what is known about the mechanism of action of both proteins and their role in vertebrate embryogenesis. Our data are discussed together with the present knowledge on other zinc-finger containing Smad interacting proteins. **Methods**: The activities and function of **SIP1** have been

analysed through documentation of expression patterns, the effect of over-expression of **SIP1** on target-gene expression, and promoter studies using Xenopus embryos. Moreover, **SIP1**/Smad complexes and their association with target promoter DNA were analyzed in biochemical studies. Results: **SIP1** is a **transcriptional repressor** displaying overlapping DNA binding specificities with δEF1. An in vivo target of **SIP1** in Xenopus is a gene required for the formation of mesoderm, Brachyury (XBra). Our data indicate that **SIP1** is required to confine XBra gene expression to the mesoderm. Furthermore, the expression pattern in Xenopus invites us to speculate that **SIP1** plays a role in specification/differentiation of neuroectoderm. Unlike δEF1, **SIP1** can bind directly to activated receptor **regulated** Smads (R-Smads) and recruit them to the DNA. This indicates that Smads may modulate the activity of **SIP1** as a **transcriptional repressor**. Conclusions: Our data point to a role of **SIP1** in developmental **processes regulated** by members of the TGFδ family such as induction of mesoderm (mediated through **activin**-like signalling) and inhibition of neuroectoderm formation (mediated by bone morphogenetic proteins [BMPs]). Whereas **SIP1** could act in **TGFβ** signal transduction by virtue of interaction with activated R-Smads, genetic studies in the mouse indicate that δEF1 may act in certain **TGFβ** pathways - i.e., BMPs and growth and differentiation **factors** (GDFs) - as well. The molecular mechanisms by which these **transcriptional repressors** act, as well as the function of the **SIP1**/Smad interaction, remain to be elucidated. Clinical Relevance: Mutations in components of the **TGFβ** signalling pathways have been associated with disease and congenital malformations. We anticipate that identification of Smad interacting **transcription factors** including **SIP1** and their targets will help us to understand the molecular basis of certain pathologies.

L17 ANSWER 30 OF 30 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-657220 [62] WPIDS
DOC. NO. NON-CPI: N2003-523633
DOC. NO. CPI: C2003-179420
TITLE: Identifying compounds that interact with **Smad protein** (co-repressor), useful for treating diseases involving negative regulation of **transforming growth factor** -beta e.g. cancer and autoimmune disease.
DERWENT CLASS: B04 C06 D16 S03
INVENTOR(S): LAUGHON, A S
PATENT ASSIGNEE(S): (LAUG-I) LAUGHON A S; (WISC) WISCONSIN ALUMNI RES FOUND
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002137662	A1	20020926	(200362)*		7
WO 2002076466	A1	20021003	(200362)	EN	

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW

AU 2002258538 A1 20021008 (200432)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002137662	A1	US 2001-810385	20010316
WO 2002076466	A1	WO 2002-US8133	20020315
AU 2002258538	A1	AU 2002-258538	20020315

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002258538	A1 Based on	WO 2002076466

PRIORITY APPLN. INFO: US 2001-810385 20010316
AN 2003-657220 [62] WPIDS
AB US2002137662 A UPAB: 20030928
NOVELTY - Identifying compounds that directly interact with a **Smad protein** or a **Smad protein** co-**repressor** to prevent protein-protein or protein-DNA interactions required for **repression** of **transcription** induced by **transforming growth factor** (**TGF**)-**beta, activin** or bone morphogenetic protein (BMP) signaling in cells, is new.

DETAILED DESCRIPTION - Identifying compounds that directly interact with a **Smad protein** or a **Smad protein** co-**repressor** to prevent protein-protein or protein-DNA interactions required for **repression** of **transcription** induced by **transforming growth factor** (**TGF**)-**beta, activin** or bone morphogenetic protein (BMP) signaling in cells comprising:

(a) determining a first level of **transcription** detected in cells in the presence of a **Smad protein** and a **CtBP** (undefined) protein before addition of a test compound;

(b) contacting the cells with the test compound; and

(c) determining a second level of **transcription** detected in cells in the presence of a **Smad protein** and a **CtBP** protein after addition of the test compound, where a decrease in the level of **repression** of **transcription** induced by the presence of the **Smad protein** and the **CtBP** protein is indicative of the ability of the test compound to interfere with **transcriptional repression** and to prevent **repression** of **transcription** that is produced by a **TGF-beta, activin**, or BMP signal in cells.

INDEPENDENT CLAIMS are also included for the following:

(1) a composition identified by the **method**; and

(2) identifying a candidate gene that is directly and negatively **regulated** by **TGF-beta** signaling pathways through a **CtBP** protein comprising:

(a) determining a first level of **TGF-beta-regulated** target gene expression in the presence of **CtBP**;

(b) determining a second level of **TGF-beta-regulated** target gene expression in the absence of the **CtBP** protein; and

(c) comparing the first level of expression with the second level of expression, where dependence of **TGF-beta-regulated** gene expression on the presence of the **CtBP** protein is indicative of the ability of the candidate gene to be directly

and negatively **regulated** by **CtBP** working in conjunction with the **Smad protein**.

ACTIVITY - Cytostatic; Immunosuppressive.

MECHANISM OF ACTION - **CtBP** inhibitor; Smad inhibitor; Negative **regulator** of **TGF-beta**. No biological data given.

USE - The compounds or genes identified through such assays would be useful in the development of drugs and therapeutics for treatment of cancer, autoimmune diseases, and other hereditary diseases that involve negative **regulation** by **TGF-beta** pathways.

Dwg.0/8

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=> d his ful

     FILE 'REGISTRY' ENTERED AT 16:04:55 ON 23 JUL 2004
                  E ACTIVIN/CN
L1                3 SEA ABB=ON  ACTIVIN/CN
                  E TGF-BETA/CN
                  E SMAD PROTEIN/CN

     FILE 'HCAPLUS' ENTERED AT 16:05:39 ON 23 JUL 2004
L2           233478 SEA ABB=ON  ?TRANSCRIPT?(L)(?REPRES? OR ?FACTOR? OR ?REGULAT?)
L3             4862 SEA ABB=ON  L2 AND (?SMAD?(W)(?PROTEIN? OR ?REPRESSOR?) OR
                    DNA?(W)?BIND?(W)?PROTEIN?)
L4              847 SEA ABB=ON  L3 AND (TGF-BETA OR L1 OR ?ACTIVIN? OR ?DROSOPHILA?
                    )
L5              205 SEA ABB=ON  L4 AND (?BONE?(W)?MORPHOGEN?(W)?PROTEIN? OR
                    ?PROTEIN?(W)?MOTIF?)
L6              127 SEA ABB=ON  L5 AND (?TRANSFORM?(W)?GROWTH?(W)?FACTOR OR
                    ?NEGATIV?(W)?REGULAT?)
L7                2 SEA ABB=ON  L6 AND (?CTBP? OR ?DCTBP? OR ?CTBP2? OR EVI(W)1 OR
                    ?GGIF? OR ?SIP1? OR ?SCHNURRI?)
L8                9 SEA ABB=ON  L5 AND (?CTBP? OR ?DCTBP? OR ?CTBP2? OR EVI(W)1 OR
                    ?GGIF? OR ?SIP1? OR ?SCHNURRI?)
L9               19 SEA ABB=ON  L4 AND (?CTBP? OR ?DCTBP? OR ?CTBP2? OR EVI(W)1 OR
                    ?GGIF? OR ?SIP1? OR ?SCHNURRI?)
L10               6 SEA ABB=ON  L9 AND (MAD? OR ?MEDEA?)
L11              19 SEA ABB=ON  L9 OR L10
L12               6 SEA ABB=ON  L11 AND (?METHOD? OR ?TECHNIQ? OR ?PROCES?)
L13              19 SEA ABB=ON  L11 OR L12   19 cits from CA Plus

     FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO' ENTERED AT
     16:16:51 ON 23 JUL 2004
L14             117 SEA ABB=ON  L13
L15           * 81 DUP REMOV L14 (36 DUPLICATES REMOVED)
L16               0 SEA ABB=ON  L15 AND DRUG?(W) SCREEN?
L17              30 SEA ABB=ON  L15 AND TRANSFORM?(W) GROWTH?(W) FACTOR?
                    30 cits from other d.b.'s
```

* I saved these, should you want any or all of them.

Mary Jane Ruhl
x 22524

Inventor Search

=> d ibib abs ind l17 1-5

L17 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:736875 HCAPLUS
DOCUMENT NUMBER: 137:242137
TITLE: Compositions and methods for negative regulation of **TGF-β** pathways
INVENTOR(S): **Laughon, Allen S.**
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 15 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002137662	A1	20020926	US 2001-810385	20010316
WO 2002076466	A1	20021003	WO 2002-US8133	20020315

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-810385 A 20010316

AB Methods for screening for compds. that are neg. regulators of **TGF-β** -regulated gene expression in mammalian cells are provided, including compns. identified therefrom.

IC ICM A61K031-00
ICS G01N033-53; G01N033-567
NCL 514001000
CC 1-1 (Pharmacology)
ST **TGF beta** pathway regulation drug screening
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CtBP (cytosolic T3 binding protein); compns. and screening methods for neg. regulation of **TGF-β** pathways)
IT Molecular association
(DNA-protein; compns. and screening methods for neg. regulation of **TGF-β** pathways)
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Drosophila Mad; compns. and screening methods for neg. regulation of **TGF-β** pathways)
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Drosophila Medea; compns. and screening methods for neg. regulation of **TGF-β** pathways)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Evi-1; compns. and screening methods for neg. regulation of **TGF-β** pathways)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SIP1; compns. and screening methods for neg. regulation of **TGF**

-β pathways)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Schnurri; compns. and screening methods for neg. regulation of **TGF**-β pathways)
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Smad; compns. and screening methods for neg. regulation of **TGF**-β pathways)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**TGF**-β -regulated; compns. and screening methods for neg. regulation of **TGF**-β pathways)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TGIF; compns. and screening methods for neg. regulation of **TGF**-β pathways)
IT Drug screening
Transcription, genetic
(compns. and screening methods for neg. regulation of **TGF**-β pathways)
IT Bone morphogenetic proteins
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(compns. and screening methods for neg. regulation of **TGF**-β pathways)
IT Transforming growth factors
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(β-; compns. and screening methods for neg. regulation of **TGF**-β pathways)
IT 114949-22-3, Activin
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(compns. and screening methods for neg. regulation of **TGF**-β pathways)

L17 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:411533 HCAPLUS
DOCUMENT NUMBER: 136:97165
TITLE: Repression of Dpp targets by binding of brinker to Mad sites
AUTHOR(S): Kirkpatrick, Heidi; Johnson, Kirby; **Laughon, Allen**
CORPORATE SOURCE: Laboratory of Genetics, University of Wisconsin, Madison, WI, 53706, USA
SOURCE: Journal of Biological Chemistry (2001), 276(21), 18216-18222
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Signaling by decapentaplegic (Dpp), a Drosophila member of the transforming growth factor (**TGF**) β superfamily of growth factors, has recently been shown to activate targets such as vestigial (vg) indirectly through neg. regulation of brinker (brk). Here we show that the Brk protein functions as a repressor by binding to Dpp response elements. The Brk DNA binding activity was localized to an amino-terminal region containing a putative homeodomain. Brk bound to a Dpp

response element of the Ultrabithorax (Ubx) midgut enhancer at a sequence that overlaps a binding site for the Smad protein, Mothers Against Dpp (Mad). Furthermore, Brk was able to compete with Mad for occupancy of this binding site. This recognition of overlapping binding sites provides a potential explanation for why the G/C-rich Mad binding site consensus differs the Smad3/Smad4 binding site consensus. We also found that the Dpp response element from Ubx was more sensitive than the vg quadrant enhancer to repression by Brk. This difference correlates with short-range activation of Ubx by Dpp in the visceral mesoderm, whereas vg exhibits a long-range response to Dpp in the wing imaginal disk, indicating that Brk binding sites may play a critical role in limiting thresholds for activation by Dpp. Finally, we provide evidence that Brk is capable of functioning as an active repressor. Thus, whereas Brk and Mad compete for regulation of Ubx and vg, Brk may regulate other Dpp targets without direct involvement of Mad.

CC 3-4 (Biochemical Genetics)
Section cross-reference(s): 12

ST Drosophila brk protein decapentaplegic repression

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(UBX; repression of Dpp targets by binding of brinker to Mad sites)

IT Genetic element
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Ubx; repression of Dpp targets by binding of brinker to Mad sites)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(brk; repression of Dpp targets by binding of brinker to Mad sites)

IT Genetic element
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(decapentaplegic response; repression of Dpp targets by binding of brinker to Mad sites)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene brk; repression of Dpp targets by binding of brinker to Mad sites)

IT Drosophila melanogaster
(repression of Dpp targets by binding of brinker to Mad sites)

IT Transcriptional regulation
(repression; repression of Dpp targets by binding of brinker to Mad sites)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(vg; repression of Dpp targets by binding of brinker to Mad sites)

IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β-, decapentaplegic; repression of Dpp targets by binding of brinker to Mad sites)

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:219108 HCAPLUS
DOCUMENT NUMBER: 132:260665
TITLE: Compositions and methods for identifying and testing **TGF-β** pathway agonists and antagonists
INVENTOR(S): **Laughon, Allen**; Johnson, Kirby; Kim, Jaeseob
PATENT ASSIGNEE(S): Ophidian Pharmaceuticals, Inc., USA
SOURCE: U.S., 50 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6046165	A	20000404	US 1997-880729	19970623

PRIORITY APPLN. INFO.: US 1997-880729 19970623

AB The invention provides compns. and methods of identifying and testing **TGF-β** pathway agonists and antagonists, and in particular compns. comprising Mothers against DPP (MAD) proteins and related Smad polypeptides which exhibit sequence-specific DNA-binding activity. The invention also provides novel DNA sequences (SEQ ID NO:19); (SEQ ID NO:20); (SEQ ID NO:21) that are bound with high affinity by Drosophila MAD protein. This protein is useful for identifying compds. that will enhance or interfere with MAD protein-DNA binding.

IC ICM A61K037-00
ICS A61K031-70; A01N043-04; C07K014-00

NCL 514012000

CC 1-1 (Pharmacology)

ST transforming growth factor beta modulator screening

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MAD (Mothers against DPP); compns. and methods for identifying and testing **TGF-β** pathway agonists and antagonists)

IT Drosophila
(MAD protein of; compns. and methods for identifying and testing **TGF-β** pathway agonists and antagonists)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Smad; compns. and methods for identifying and testing **TGF-β** pathway agonists and antagonists)

IT DNA sequences
Drug screening
(compns. and methods for identifying and testing **TGF-β** pathway agonists and antagonists)

IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β-, agonists and antagonists; compns. and methods for identifying and testing **TGF-β** pathway agonists and antagonists)

IT 118349-06-7 263138-64-3 263138-65-4
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(MAD protein binding of; compns. and methods for identifying and testing **TGF-β** pathway agonists and antagonists)

IT 263379-87-9, 1: PN: US6046165 SEQID: 5 unclaimed DNA 263379-88-0, 2: PN: US6046165 SEQID: 6 unclaimed DNA 263379-89-1, 3: PN: US6046165 SEQID: 7 unclaimed DNA 263379-90-4, 4: PN: US6046165 SEQID: 8 unclaimed DNA 263379-91-5, 6: PN: US6046165 SEQID: 10 unclaimed DNA 263379-92-6, 7: PN: US6046165 SEQID: 11 unclaimed DNA 263379-93-7, 8: PN: US6046165 SEQID: 12 unclaimed DNA 263379-94-8, 9: PN: US6046165 SEQID: 13 unclaimed DNA 263379-95-9 263379-96-0 263379-97-1 263379-98-2 263379-99-3 263380-00-3, 15: PN: US6046165 SEQID: 1 unclaimed DNA 263380-01-4, 16: PN: US6046165 SEQID: 2 unclaimed DNA 263380-02-5, 17:

PN: US6046165 SEQID: 3 unclaimed DNA 263380-03-6 263380-04-7 263380-05-8 263380-06-9 263380-07-0 263380-08-1 263380-09-2 263380-10-5 263380-11-6 263380-12-7 263380-13-8 263380-14-9, 32: PN: US6046165 SEQID: 4 unclaimed DNA 263397-73-5, 5: PN: US6046165 SEQID: 9 unclaimed DNA
RL: PRP (Properties)
(unclaimed nucleotide sequence; compns. and methods for identifying and testing **TGF**-β pathway agonists and antagonists)

REFERENCE COUNT: 103 THERE ARE 103 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:467078 HCAPLUS
DOCUMENT NUMBER: 131:224368
TITLE: Interaction of Smad complexes with tripartite DNA-binding sites
AUTHOR(S): Johnson, Kirby; Kirkpatrick, Heidi; Comer, Allen; Hoffmann, F. Michael; **Laughon, Allen**
CORPORATE SOURCE: Laboratory of Genetics, University of Wisconsin-Madison, Madison, WI, 53706, USA
SOURCE: Journal of Biological Chemistry (1999), 274(29), 20709-20716
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The Smad family of transcription factors function as effectors of transforming growth factor-β signaling pathways. Smads form heteromultimers capable of contacting DNA through the amino-terminal MH1 domain. The MH1 domains of Smad3 and Smad4 have been shown to bind to the sequence 5'-GTCT-3'. Here the authors show that Smad3 and Smad4 complexes can contact three abutting GTCT sequences and that arrays of such sites elevate reporter expression relative to arrays of binding sites containing only two GTCTs. Smad3/4 complexes bound synergistically to probes containing two of the four possible arrangements of three GTCT sequences and showed a correlated ability to synergistically activate transcription through these sites. Purified Smad3 and Smad4 were both able to contact three abutting GTCT sequences and reporter expts. indicated that either protein could mediate contact with all three GTCTs. In contrast, the Smad4 MH1 domain was essential for reporter activation in combination with Smad1. Together, these results show that Smad complexes are flexible in their ability to interact with abutting GTCT triplets. In contrast, Smads have high affinity for only one orientation of abutting GTCT pairs. Functional Smad-binding sites within several native response elements contain degenerate GTCT triplets, suggesting that trimeric Smad-DNA interaction may be relevant in vivo.
CC 3-4 (Biochemical Genetics)
ST Smad3 Smad4 complex DNA binding GTCT element transcription activation
IT Genetic element
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(GTCT; as Smad3/4 complex binding site; Smad complexes capable of contacting up to three abutting Smad boxes and contact can stabilize binding and enhance transcription activation)
IT Transcription factors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study);

PROC (Process)
(Smad3/4 complexes; Smad complexes capable of contacting up to three abutting Smad boxes and contact can stabilize binding and enhance transcription activation)
IT Protein motifs
(Smad4 MH1 domain required for transcription activation; Smad complexes capable of contacting up to three abutting Smad boxes and contact can stabilize binding and enhance transcription activation)
IT Transcriptional regulation
(activation; Smad complexes capable of contacting up to three abutting Smad boxes and contact can stabilize binding and enhance transcription activation)
IT Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(complexes, Smad3/4 complexes; Smad complexes capable of contacting up to three abutting Smad boxes and contact can stabilize binding and enhance transcription activation)
IT Genetic element
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(detection of Smad binding sites within **TGF-β** responsive site; Smad complexes capable of contacting up to three abutting Smad boxes and contact can stabilize binding and enhance transcription activation)
IT Genetic element
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(detection of Smad binding sites within activin response element; Smad complexes capable of contacting up to three abutting Smad boxes and contact can stabilize binding and enhance transcription activation)
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:909240 HCAPLUS
DOCUMENT NUMBER: 124:25918
TITLE: A Drosophila protein related to the human zinc finger transcription factor PRDII/MBPI/HIV-EP1 is required for dpp signaling
AUTHOR(S): Staehling-Hampton, Karen; **Laughon, Allen S.**; Hoffmann, F. Michael
CORPORATE SOURCE: Lab. Genet., Univ. Wisconsin Med. Sch., Madison, WI, 43706, USA
SOURCE: Development (Cambridge, United Kingdom) (1995), 121(10), 3393-403
CODEN: DEVPED; ISSN: 0950-1991
PUBLISHER: Company of Biologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Little is known about the signal transduction pathways by which cells respond to mammalian **TGF-β** s or to decapentaplegic (dpp), a Drosophila **TGF-β** -related factor. The genetic and mol. characterization of Drosophila schnurri (shn), a putative transcription factor implicated in dpp signaling, is described. The shn protein has 8 zinc fingers and is related to a human transcription factor, PRDII/MBPI/HIV-EP1, that binds to nuclear factor-κB-binding sites and activates transcription from the HIV long terminal repeat (LTR). Shn mRNA is expressed in a dynamic pattern in the embryo that includes most of

the known target tissues of dpp, including the dorsal blastoderm, the mesodermal germ layer, and parasegments 4 and 7 of the midgut. Mutations in shn affect several developmental processes regulated by dpp, including induction of visceral mesoderm cell fate, dorsal/ventral patterning of the lateral ectoderm, and wing vein formation. Absence of shn function blocks the expanded expression of the homeodomain protein bagpipe in the embryonic mesoderm caused by ectopic dpp expression, illustrating a requirement for shn function downstream of dpp action. Thus, shn function is critical for cells to respond properly to dpp and propose that shn protein is the first identified downstream component of the signal transduction pathway used by dpp and its receptors.

CC 12-3 (Nonmammalian Biochemistry)
Section cross-reference(s): 3, 6

ST gene schnurri transcription factor Drosophila development; decapentaplegic gene signaling schnurri Drosophila; sequence gene schnurri protein cDNA Drosophila

IT Development, nonmammalian
Drosophila melanogaster
Signal transduction, biological
(Drosophila schnurri protein related to human zinc finger transcription factor PRDII/MBPI/HIV-EP1 is required for decapentaplegic signaling)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene bagpipe; Drosophila schnurri protein related to human zinc finger transcription factor PRDII/MBPI/HIV-EP1 is required for decapentaplegic signaling)

IT Ribonucleic acid formation factors
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(gene schnurri; Drosophila schnurri protein related to human zinc finger transcription factor PRDII/MBPI/HIV-EP1 is required for decapentaplegic signaling)

IT Protein sequences
(of gene schnurri transcription factor from Drosophila melanogaster)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(schnurri; Drosophila schnurri protein related to human zinc finger transcription factor PRDII/MBPI/HIV-EP1 is required for decapentaplegic signaling)

IT Deoxyribonucleic acid sequences
(complementary, for gene schnurri transcription factor from Drosophila melanogaster)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(decapentaplegic, Drosophila schnurri protein related to human zinc finger transcription factor PRDII/MBPI/HIV-EP1 is required for decapentaplegic signaling)

IT Embryo
(mesoderm, Drosophila schnurri protein related to human zinc finger transcription factor PRDII/MBPI/HIV-EP1 is required for decapentaplegic signaling)

IT 167976-42-3
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(amino acid sequence; Drosophila schnurri protein related to human zinc finger transcription factor PRDII/MBPI/HIV-EP1 is required for decapentaplegic signaling)

IT 168146-66-5, GenBank U31368
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; Drosophila schnurri protein related to human zinc finger transcription factor PRDII/MBPI/HIV-EP1 is required for decapentaplegic signaling)